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11/03/2010

# **DRUG USE IN OUTPATIENT CHILDREN: EPIDEMIOLOGICAL EVALUATIONS**

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## ABSTRACT

**Background.** Pharmacoepidemiology can be a useful tool for evaluating the appropriateness of drug prescriptions and for estimating therapeutic needs. In particular, pharmacoepidemiology can be valuable in the paediatric setting, which is characterized by the availability of only limited information on the safety and effectiveness of drug use.

**Methods.** Data collected in regional and multiregional administrative prescription databases were analysed. Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group. The number of packages of medications (boxes) was used as indicator of drug consumption. Univariate and multivariate analyses were performed with the aim to identify the determinants of drug prescriptions.

**Results.** Drug utilization studies reported quantitative and qualitative differences between countries in drug prescription to children and adolescents. In particular, Italian children have a threefold greater chance of receiving an antibiotic or an anti-asthmatic compared with children living in the Netherlands.

Large differences also were found within Italy between different geographical settings, with prevalence ranging between 57.3% in northern Italy and 68.3% in southern Italy. Prevalence varied also between the local health units (LHUs) of a single region and between district of a single LHU. In the Lombardy Region prevalence ranged between 38.4% in Milan and 54.8% in Brescia, and the residence of the child was one of the main determinant of drug exposure.

**Conclusions.** The studies described in this thesis suggest that pharmacoepidemiology is a valuable tool for monitoring the appropriateness of drug prescribing. However, the epidemiological evaluation of drug prescriptions in children should be improved with regards to the methodological quality of studies.

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### **III. INTRODUCTION**

Drug therapy is widely used in the treatment of diseases in childhood and studies of drugs are important.<sup>1</sup> Many drugs prescribed to children are originally developed for adults, and they are often prescribed on an unlicensed or off-label basis by extrapolating data for adults, without conducting any paediatric study.<sup>2</sup> In this regard it is to be recognised that only 35% of commercially available drugs in Europe are authorized for use in children.<sup>3</sup> The extent of unlicensed or off-label drug use ranges between 16% and 97% of children, depending on the country, the setting (community or hospital) and the disease.<sup>2</sup> The off label drug use exposes children to an increased risk of adverse drug reactions.<sup>4</sup>

Many factors contribute to the fact that children do not participate in clinical trials, in particular ethical and financial reasons; resources and research capabilities; and regulatory guidelines and constraints.<sup>5-7</sup> In the last few years, many initiatives have been introduced at an international level to guarantee safe and effective therapies for children.<sup>8,9</sup> In 1997, the Food and Drug Administration introduced the Food and Drug Modernization Act, that was followed by the Best Pharmaceuticals for Children Act. Closely linked to this legislation is the Pediatric Rule (1998) which requires the industry to perform research in the paediatric population.

The European Union adopted a quite similar legislation (Regulation on Medicinal Products for Paediatric Use) that entered into force in on 26 January 2007.

Despite these initiatives, however, a lack of information on safety and efficacy of drugs in childhood still exists.<sup>5</sup> In such a context, pharmacoepidemiology can be a useful tool that with the appropriate methodologies, can improve the effectiveness and efficiency of health care interventions.<sup>10</sup> Drug utilization studies in children may be used to

identify the major therapeutic problems in the population. Moreover, rational drug therapy is important for all drug users, but it is of paramount importance for children.

In this regard, a review of drug utilization studies published between 1988 and 1993 found eight studies that evaluated drug prescriptions to outpatient children. Differences in prescribing pattern between countries were found, with an average number of drugs per child ranging between 0.7 and 3.0.<sup>11</sup>

Large differences were found regarding sample size, data sources, and age of children, making the comparison of the results difficult. The review highlighted the lack of a systematic approach in the evaluation of drug use in children and called for more studies to be performed. This thesis is an attempt to evaluate drug use in children in more detail.

For doing so, a systematic review of the literature was performed with the aim to analyse the characteristics (design, methods, population) and the results of epidemiological studies evaluating drug prescription to children outside the hospital published since 1994 (after the period covered by the review cited above). A comparison of the prescribing pattern between countries was performed when possible. For estimating the profile of drug use in Italian outpatient children, two different administrative data sources were analysed: a large multiregional prescription database (representing nearly 10 million individuals, 17% of the Italian population) and a regional administrative prescription database (Lombardy region prescription database). Different variables were considered in the analysis of drug prescription profile, in particular: gender and age of the youth, drug, setting, and prescriber.



Finally, an in-depth evaluation of the prescription profile of two drug classes was performed: psychotropic drugs, for which safety concerns have been raised, and anti-asthmatics, that were used as indirect indices of prevalence of asthma, the most common chronic disease in childhood.

#### **IV.**

### **A REVIEW OF THE LITERATURE**

## **A SEARCH STRATEGY AND DATA EXTRACTION**

The literature search was performed in MEDLINE and EMBASE databases regarding studies of drug use in paediatric outpatients published from January 1994 to December 2008. The MeSH terms used in the search strategy were: drug utilization/prescription/pharmacoepidemiology; infant /child/adolescent/paediatrics. The search was limited for papers in English language. Letters, comments, editorials were excluded. The titles and abstracts were screened independently by two reviewers to assess the relevance of the studies. Contrasting results were reviewed by a third person. Studies involving adult population, inpatient children or children attending the emergency department, evaluating adverse drug reactions, the costs or the health care resource utilization, were excluded.

For each study, data concerning the type of the study, the source of the data, country, sample size, age of children and drugs monitored were collected, and a descriptive analysis was performed.

An in-depth analysis was performed taking into account studies that analysed all drug prescriptions.

A second search was focused on antibiotics, anti-asthmatics (i.e. inhaled steroids; short-acting adrenergic  $\beta_2$  agonists; long-acting adrenergic  $\beta_2$  agonists; leukotriene receptor antagonists) and antidepressants. These drugs were chosen on the basis of the results of the first search, since the majority of the retrieved studies concerned these therapeutic classes.

For these drugs, the literature search was not restricted to English language but was limited to the 2000-2008 period, with the aim to analyse the most recent studies. The

MeSH search terms and additional keywords used in the search strategy were: drug utilization/prescriptions/pharmacoepidemiology; child/infant/adolescent/paediatrics; anti-bacterial agents/antibiotic agents/antidepressant agent/anti-asthmatic agent.

Manual searches of bibliographies were also conducted to identify additional pertinent studies. Books and proceedings from meetings and congresses were not considered.

The references retrieved were collected and analysed using the software program Reference Manager, version 11 (Institute for Scientific Information, Berkeley, California).

Annual prevalence (number of youths who received at least one prescription per 100 individuals in the population during a year) and prescription rate (average number of prescription per person) were used as indicators. When a study analysed more than one year, data concerning the last available year period were taken into account.

Meta-analytic weighted average and 95%CIs of the prevalence rate of drug prescription were estimated using a random effect regression model to take into account the heterogeneity of the various studies.<sup>12</sup>

## **B. ALL DRUG PRESCRIPTIONS**

### **1. Search results**

A total of 980 articles were retrieved from the literature databases: 464 from EMBASE and 422 from Medline, and 94 from both (Figure 1).

**Figure 1 – Procedure for the bibliographic search**

<b>MEDLINE</b>	<b>MeSH search terms</b>	<b>EMBASE</b>
30198	Drug utilization OR pharmacoepidemiology OR Drug prescriptions	57233
21978	Limit humans, English	35851
16200	Published since 01/01/1994	33217
2954	All child	3543
2490	NOT letter, editorial, comment, practice guideline, randomized controlled trial	2872
910	NOT Adult	1175
710	NOT Hospitals OR Emergency Service, Hospital OR Hospitalization OR Child, Hospitalized OR Adolescent, Hospitalized OR Inpatients OR Hospital Units OR Surgical Procedures, Operative	802
674	NOT pregnancy OR lactation	776
652	NOT addictive behavior OR substance related disorders	761
640	NOT poisoning	731
635	NOT complementary therapies	717
623	NOT vaccine OR immunization	695
537	NOT diagnosis	629
528	NOT dental care	625
<b>516</b>	NOT side effect	<b>558</b>

In all, 734 papers were excluded because they were not pertinent. Moreover, 99 of the 246 remaining studies involved children with particular conditions, mainly respiratory tract infections (37%), mental disorders (22%) and asthma (20%), and were therefore not taken into account in the analysis. The same was done for 10 studies evaluating off-label/unlicensed drug use and for 9 studies analysing the prescriptions of a single drug.

## **2. Characteristic of the drug utilization studies**

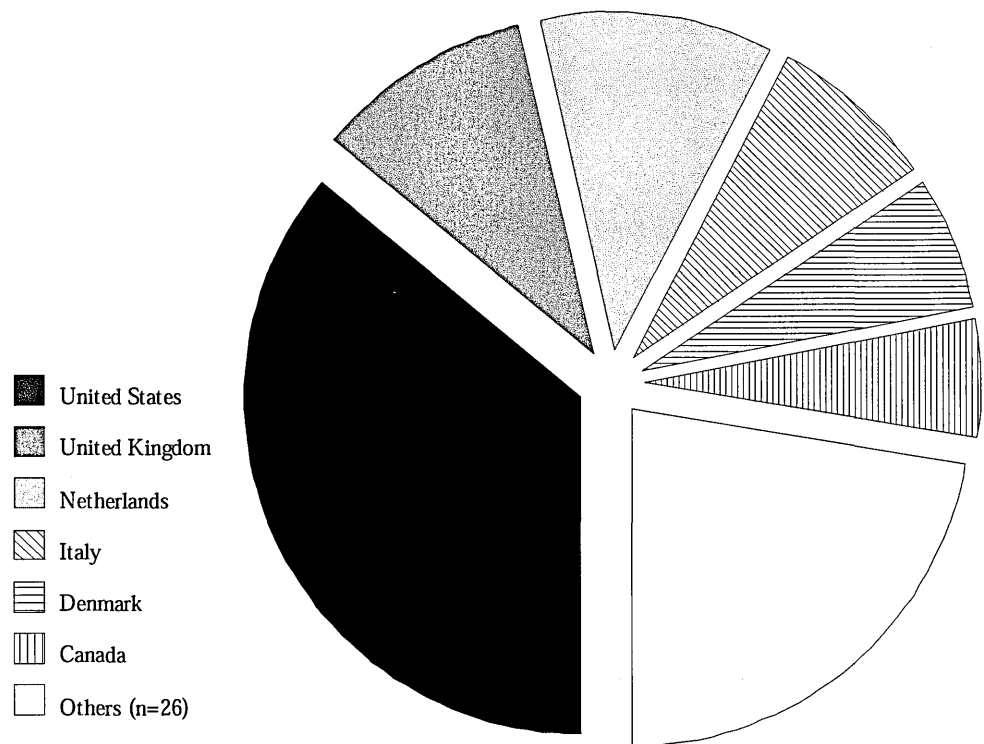
A total of 128 drug utilization studies was therefore analysed. These studies were published in 59 journals, 23 of which published more than one article. The first ten journals in order of papers covered 46% of the retrieved articles. The European Journal Clinical Pharmacology was the first journal in order of published papers (10), followed by Acta Paediatrica, Pharmacoepidemiology and Drug Safety, and Psychiatric Services (7 papers each).

The distribution of papers per year of publication ranged from 1 in 1994 to 18 in 2006 and 2007 (mean: 8.5). Only 19 studies (17%) were published before 2000, while 74 studies were published in the 2004-2008 period. The 128 articles were published by 459 authors, 83 (18%) of which appeared in at least two papers. In all, 14 authors published 4 or more papers. These authors belong to a few groups particularly involved in the field of paediatric pharmacoepidemiology that are based in Baltimore (USA), Milan (Italy), Groningen (The Netherlands), London, and Aberdeen (UK), and accounted for 28 studies (22% of the total).

The 128 studies involved 32 countries, 14 of which were involved in more than one study. In all, 57 out of 128 studies (44%) were performed in Europe and 51 (40%) in North America. Only 8 studies involved developing countries.

35% of the studies involved the United States, followed by the Netherlands (11%), the United Kingdom (10%), Italy (8%), and Denmark (6%) (Figure 2). In all, 6 studies were multinational.

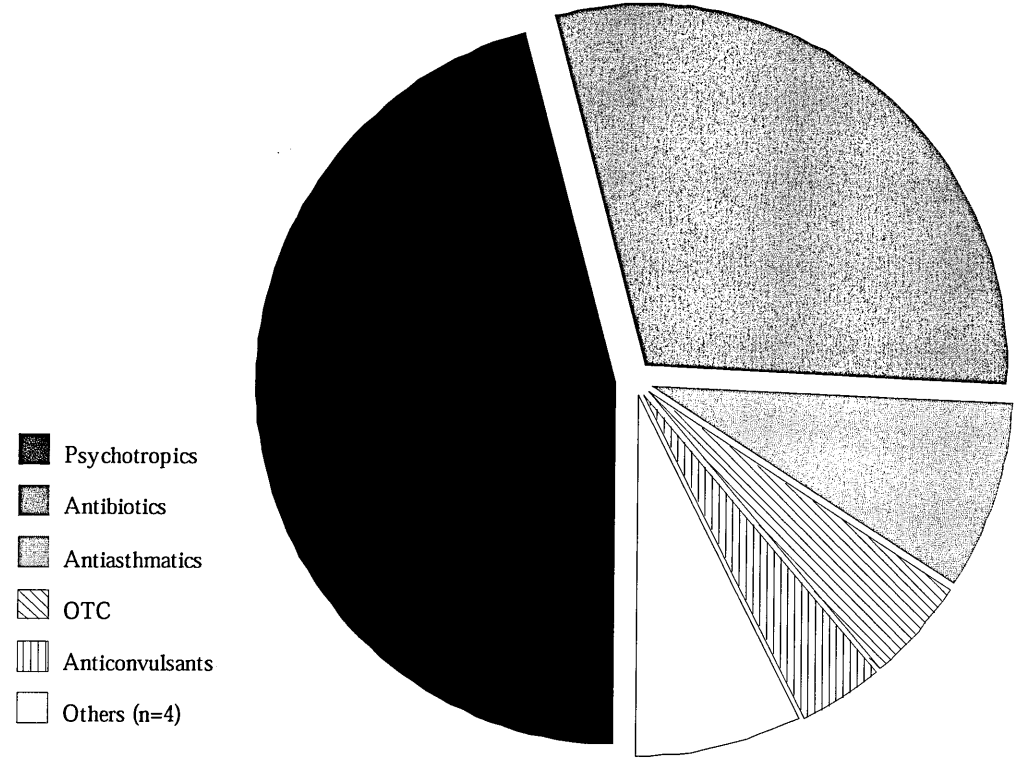
**Figure 2 – Distribution of the drug utilization studies by country.**



The data sources were mainly national or regional prescription databases (28% of the studies), general practitioner or paediatrician practices (19%), national surveys (e.g. National Ambulatory Medical Care Survey, Medical Expenditure Panel Survey) (14%), Health Maintenance Organizations (HMO) and Medicaid/national health insurance (12% each), and questionnaires administered to patients or parents (10%).

A total of 107 studies focused on a specific drug class. In particular, 49 studies (46%) concerned psychotropic drug prescriptions, 32 (30%) antibiotics, 9 (8%) anti-asthmatics, 5 (5%) over the counter drugs, and 4 (4%) anticonvulsants. (Figure 3).

**Figure 3 – Distribution of the drug utilization studies by drug class.**





**Table 1 – Characteristics of the studies**

Ref.	Study type	Data source	Country	Year	Duration	Age (yr)	N children
13	Prospective	Prescription DB	Bahrain	2004 (May)	2 weeks	1-12 mo	-
14	Survey	Questionnaires	UK	1991		0-6 mo	6973
15	Survey	GP	Egypt	n.r.	1 month	< 1	300
16	Retrospective	Health facility DB	Kenya	1995-1996	2 years	< 5	14267
17	Retrospective	GP	Pakistan	1992 (Apr-Dec)	9 months	< 5	2433
18	Cohort	GP	Greenland	1996-1998	2 years	< 5	280
19	Prospective	GP	Nigeria	2004 (Jan-Apr)	4 months	< 5	790
20	Survey	Questionnaires	Tanzania	2001(Aug-Sep)	2 months	< 5	612
21	Prospective	GP	New Zealand	2000	1 year	13-19	20216
22	Survey	Questionnaires	Germany	1997	2 weeks	15 - 17	56

23	Retrospective	Prescription DB	Italy	2006	1 year	<14	923,353
24	CrossSectional	Prescription DB	Greenland	1991	1 year	< 15	2836
25	Retrospective	Prescription DB	Greenland	2001	1 year	< 15	3296
26	CrossSectional	Prescription DB	Denmark	1997	1 year	< 16	95,189
27	CrossSectional	Prescription DB	Netherlands	1998	1 year	< 17	25,020
28	CrossSectional	Prescription DB	Denmark	1998	1 year	< 19	104,897
29	Prospective	GP	Italy	1998 (Apr-June)	3 months	<12	9917
30	CrossSectional	GP	Norway	1988-1989	1 year	< 13	7299
31	CrossSectional	GP	Multi	n.r.	4-7 months	< 14	12,264
32	Prospective	GP	Multi	2000-2005	6 years	< 19	675,868
33	Retrospective	HMO	US	1992-1993	1 year	< 18	3144

### 3. Characteristic of studies evaluating all drug prescriptions

A total of 21 studies evaluated all the drugs prescribed (Table 1).<sup>13-33</sup> These studies involved 21 countries: 5 studies were performed in Denmark (3 of which were in Greenland), 3 studies in Italy, and 2 studies each in the Netherlands and the UK. Two studies were multinational: one compared data collected in 5 different countries,<sup>31</sup> and one in three European countries.<sup>32</sup> The sources of data were represented by paediatricians/general practitioners (9 studies), national and regional prescription databases (7), questionnaires (3), HMO and health facilities databases (1 each).

The studies involved from 56 to 923,353 children. Eleven studies evaluated drug prescriptions in the entire paediatric population, with an upper age limit ranging from 13 to 19 years,<sup>23-33</sup> while 10 studies were focused only on a specific age group: 3 involved only infants,<sup>13-15</sup> 5 only pre-schoolers,<sup>16-20</sup> and two only adolescents.<sup>21,22</sup> The observation periods ranged between 1988 and 2006. Only seven studies (33%) evaluated data collected after 2000.<sup>13,19-21,23,25,32</sup>

#### *a) Infants*

Only one out of 3 studies involving infants reported the prevalence of drug prescription: 96% of infants aged less than 6 months were given at least one drug, and the drug most commonly used was paracetamol (84% of the infants), followed by teething gel (54%).<sup>14</sup> Another study analysed 2282 prescriptions dispensed to infants by 20 health care centers in Bahrain. Paracetamol was the most frequently prescribed drug and accounted for 58% of prescriptions, followed by saline nasal drops (32% of prescriptions).<sup>13</sup>

A study performed in Alexandria, Egypt, evaluated the use of non-prescribed medications. During a one month observation period, 24.6% of the mothers

administered non prescribed medications to their children, in particular antispasmodics (47%), antipyretics (13%), and cough and cold medications (8%).

*b) Pre-schoolers*

Studies involving only pre-schoolers were performed almost exclusively in developing countries (4 out of 5 papers), and three were performed in Africa. None of the studies reported the prevalence of drug prescriptions and only two reported the average number of drugs per patient, but in a non-comparable manner.<sup>16,18</sup>

Antimalarials, antibiotics, and analgesics/antipyretics were the most used drugs in the three studies performed in African countries.<sup>16,19,20</sup> Antimalarials accounted for 24% of drugs purchased at pharmacies or drug stores in the Kibaha district, Tanzania,<sup>20</sup> while a study performed in Nigeria reported that these drugs were prescribed to 65% of children <5 years old attending an outpatient clinic.<sup>19</sup> In these two studies, antibiotics covered 31% of purchased drugs and 54% of patients, respectively. Chloroquine was prescribed in 70% of sick patient visits in health facilities in Kenya, penicillin in 61% and antipyretics in 59%.<sup>16</sup>

A quite different prescribing profile was observed in the two studies performed outside Africa. Antibiotics were prescribed in 49%, and paracetamol in 25% of encounters in a study performed in Pakistan.<sup>17</sup> Antibiotics were also the most frequently prescribed drugs in pre-school aged children in Greenland (50% of prescriptions), followed by respiratory drugs (21%) and dermatologicals (20%).<sup>18</sup>

### *c) Adolescents*

The prevalence of drug use in adolescents was 56% in a survey involving secondary school students in Germany<sup>22</sup> and 70% in a study that analysed prescriptions made by general practitioners in New Zealand.<sup>21</sup>

The drugs most commonly used by the adolescents in the German study were antipyretics (35% of the adolescents), cough and cold medicines (23%), and contraceptive agents and urologicals (13%).<sup>22</sup> In all, 28% of the prescriptions monitored in New Zealand were for respiratory system drugs, 23% for anti-infectives, and 10% for contraceptive agents and urologicals.<sup>21</sup>

### *d) Overall paediatric population*

The annual prevalence was reported in 9 out of 11 studies that surveyed the entire paediatric population, and ranged from 51% in Denmark to 70% in Greenland, while the prescription rate (i.e. the average number of prescriptions per child in the population) ranged from 0.8 in Norway to 3.2 in the United States (Table 2). No correlation was found between prevalence and prescription rates. A total of 7 studies reported the prevalence trend by age. In all these studies, the highest prevalence was observed in the preschoolers and decreased in children > 6 years.<sup>23,25-29,33</sup>

However, in Denmark, the Netherlands and the United States the peak in prevalence was observed in children < 2 years old, ranging from 75 to 90%,<sup>26-28,33</sup> while in Italy and Greenland the peak was reported in children 3-5 years old (72-80%).<sup>23,25,29</sup>

Antibiotics were the most frequently prescribed drugs, accounting for 20-33% of the prescriptions dispensed to children, followed by anti-asthmatics (10-25% of the total prescriptions) and analgesics (10-16%).

Four studies reported the most frequently prescribed drugs,<sup>23,25,29,32</sup> but only in two was the prevalence of drug prescription reported. Paracetamol was among the 10 most frequently prescribed drugs in all the four studies, and salbutamol was reported in three out of four.

#### *e) Meta-analysis*

Only four studies were comparable in terms of data source (prescription databases) and age and were thus selected for the meta-analysis.<sup>23,25-27</sup> The meta-analytic estimated average, adjusted and weighted by sample size, was 60.4% (95%CI 54.0-66.8%). The estimated average prevalence of antibiotics was 33.9% (95%CI 13.5-54.3%), while that of anti-asthmatics was 14.5% (95%CI 4.5-24.2%)

Table 2 – Prevalence and prescription rates

Ref.	Data source	Country	Year	Age (years)	N. children	Prevalence		Prescription rate*	Population
						%	95% CI		
29	GP	Italy	1998	<12	9917	64.7	63.8-65.6	0.9 (1.3)	Contacts
30	GP	Norway	1988-1989	< 13	7299	60.1	59.0-61.2	0.8 (1.4)	Contacts
31	GP	Spain	n.r.	< 14	4611	n.a.		1.5 (1.7) drugs	Contacts
31	GP	France	n.r.	< 14	1990	n.a.		2.7 (2.8) drugs	Contacts
31	GP	Russia	n.r.	< 14	2194	n.a.		2.9 (3.1) drugs	Contacts
31	GP	Bulgaria	n.r.	< 14	1874	n.a.		2.6 (2.7) drugs	Contacts
31	GP	Slovakia	n.r.	< 14	1495	n.a.		2.6 (2.7) drugs	Contacts
32	GP	Italy	2000-2005	< 15	406,156 <sup>†</sup>	n.r.	-	2.5	Contacts
32	GP	Netherlands	2000-2005	< 19	282,869 <sup>†</sup>	n.r.	-	1.5	Contacts
32	GP	UK	2000-2005	< 19	1,645,828 <sup>†</sup>	n.r.	-	2.5	Contacts
33	HMO	USA	1992-1993	< 18	3144	59.1	57.2-60.9	3.2 (5.3)	Enrollees

23	Prescription DB Italy	2006	< 14	923,353	60.8	60.7-60.9	1.9 (3.2)	Inhabitants
24	Prescription DB Greenland	1991	< 15	2836	60.0	58.3-61.9	2.2 (3.7)	Inhabitants
25	Prescription DB Greenland	2001	< 15	3296	70.4	68.8-71.9	2.2 (3.4)	Inhabitants
26	Prescription DB Denmark	1997	< 16	95,189	50.6	50.2-50.8	1.6 (3.2)	Inhabitants
27	Prescription DB Netherlands	1998	< 17	25,020	60.0	59.4-60.6	n.r	Inhabitants
28	Prescription DB Denmark	1998	< 19	104,897	52.6	52.4-53.0	1.7 (3.3)	All

\* 0: average number of prescriptions in treated children; <sup>†</sup> Number of person years.



## **C. ANTIBIOTIC DRUG PRESCRIPTIONS**

### **1. Search results**

A total of 108 articles were retrieved from the literature databases: 53 from EMBASE and 44 from Medline, and 11 were in both. In all, 70 were excluded because they were specific to a single disease, antibiotic or drug subclass, or analysed only the quality of prescriptions. After the identification of 4 additional studies through a manual search of the references, a total of 42 surveys fitted the inclusion criteria, but, after a qualitative evaluation of pharmacoepidemiological data, a further 18 studies were excluded: 15 because they expressed data with non comparable indicators (i.e. prevalence and/or prescription rate calculated based on ambulatory visits or single disease, and drug prescription rate expressed as Defined Daily Dose) and 3 because they considered data presented in other publications<sup>26,34,35</sup> A total of 24 pharmacoepidemiological studies published during 2000-2008, including comparable data (prevalence and/or prescription rate) were therefore analysed (Table 3).

### **2.Characteristics of the studies**

A total of 9 countries were involved in the studies: Italy (5 studies), USA and the Netherlands (5 studies each), Denmark (4), Canada (3), UK (2), Germany, Sweden, and Croatia (1 study each).

The data sources were mainly physician prescription databases or regional/national prescription databases taking part in periodical health care monitoring systems (14 articles), followed by health insurance and pharmacy dispensing databases (5 articles), and only one case of a computerized, self-administered questionnaire to GPs. (Table 3).

Most of the surveys evaluated only antibiotics, while 5 included all drug categories.<sup>18,23,27,36,37</sup> A wide heterogeneity was found between studies, with regard to sample size (from a minimum of 300 to a maximum of 60 million subjects) and age classes considered. Furthermore, the studies involved child and adolescent populations (0-19 years) (Table 3), but 7 were focused on pre-school children (0-6 years), one of which involved 0-2 year old children and one 0-4 year old.

**Table 3 - Characteristics of the studies evaluating antibiotic drug prescriptions.**

Ref.	Period	Country	Age (years)	Population (N.)	Data Source	Prescription rate*
38	1993-94	Germany	≤ 6	331	Physicians	<b>0.8</b>
39	1996	US	3 m-6	46,477	National Survey	<b>1.9</b>
18	1996-98	Denmark (Greenland)	≤ 4	280	GP	<b>1.5</b>
40	1997-99	Denmark	≤ 2	5,024	Prescription DB	<b>2.2</b>
41	1999	US	< 5	~ 20 million	National Survey	<b>0.7<sup>†</sup></b>
42	2002	Sweden	≤ 6	651,954	Pharmacy dispensing DB	<b>0.8</b>
43	2004	Croatia	<6	964	Physicians	<b>n.r.</b>
44	1998	Italy	≤ 15	140,630	Prescription DB	<b>0.9</b>
45	2000	Italy	1-14	414,880	Prescription DB	<b>1.2</b>
46	2002	Italy	≤14	482,023	Prescription DB	<b>1.2</b>
47	2002	Italy	≤ 14	26,912	Prescription DB	<b>0.8</b>
23	2006	Italy	≤ 13	923,253	Prescription DB	<b>1.3</b>
27	1998	Netherlands	≤ 16	25,020	Pharmacy DB	<b>n.a.</b>

48	1998	Netherlands	≤ 16	13,426	GP	<b>0.2</b>
49	2001	Netherlands	≤ 17	76,010	GP	<b>0.2</b>
50	1999-05	Netherlands	≤ 19	115,000	Prescription DB	<b>0.3</b>
51	1999-00	USA	≤ 15	~ 60	National Survey	<b>0.5</b>
				million <sup>s</sup>		
52	2000	USA	3 m-18	~ 5000	HMO	<b>0.9</b>
53	1996-01	USA	1-14	35,028	National Survey	<b>n.r</b>
36	1999-00	Canada	≤ 17	1,031,731	HMO	<b>1.7</b>
54	2001	Canada	≤ 19	322,684	HMO	<b>0.9</b>
55	1999-03	Canada	≤ 14	n.r.	Prescriptions DB	<b>0.6</b>
37	1997	UK	≤ 12	1807	GP	<b>0.4</b>
56	1999-00	UK	≤ 16	168,396	Questionnaire	<b>n.a.</b>
55	1999-03	Denmark	≤ 14	n.r.	Prescriptions DB	<b>0.3</b>

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\*prescription per person/year; † Evaluated as number of visits with one or more antibiotic prescription(s);

### 3. Inter-country variation in prevalence and/or prescription rate.

#### *a) Pre-school population*

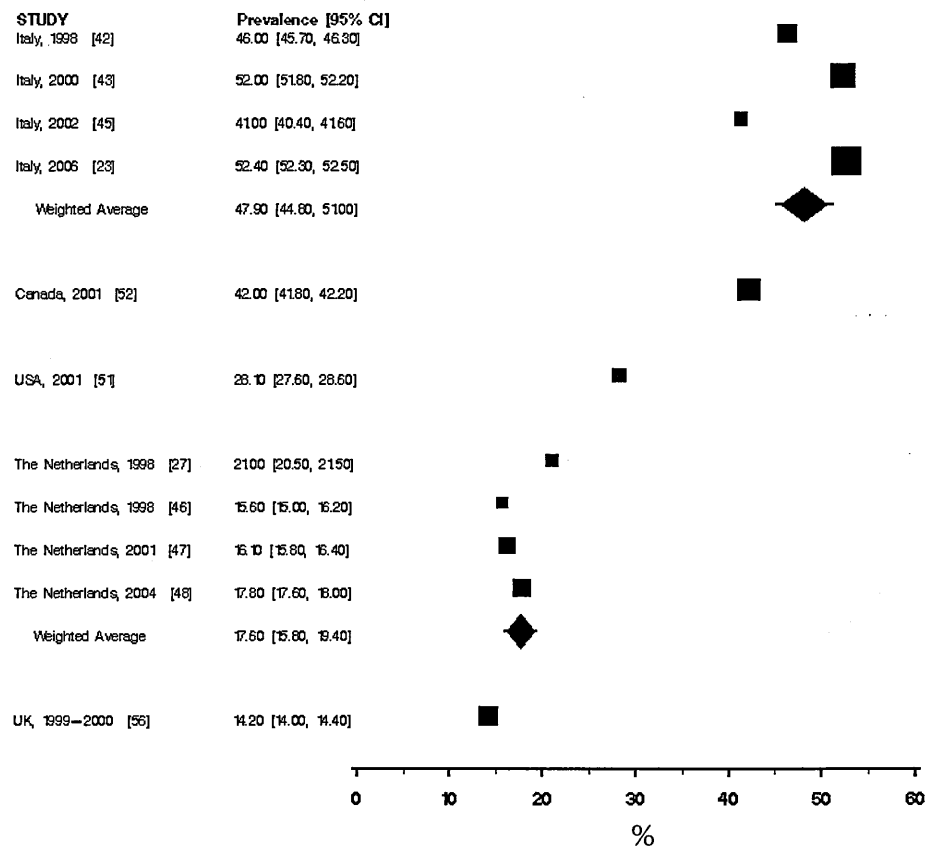
In the pre-school population, the prescription prevalence (reported by only two studies) decreased from 71.8% for 0-2 years old children to 42.9% for 0-6 years old. The prescription rate decreased from 2.2-1.5 prescriptions/person/year in the first few years of life (respectively for 0-2 year and 0-4 year old children) to 1.9-0.8 prescriptions/person/year, considering the overall pre-school population (respectively 3 months-6 year and 0-6 year old children) (Table 3). A decrease in USA antibiotic use for the pre-school population emerged when data from 1996 to 2000 were reviewed, with a decline in prescription rate from 1.9 to 0.7 prescriptions/person/year.

*b) Overall paediatric population*

Taking into account the 19 studies involving either pre-school or school-aged children, (and in 8 cases also adolescents), differences in antibiotic use emerged among the six countries considered, both quantitatively and qualitatively (Table 3). In general, two prescribing patterns can be identified, with some countries with high antibiotic prescribing levels (Italy and Canada), with prevalence ranging from 42 to 52.4% (prescription rate: 0.8-1.3 prescriptions/person/year), and countries with low antibiotic prescribing levels (the Netherlands and the UK), with prevalence ranging from 14.2 to 21.0% (prescription rate: 0.2-0.4 prescriptions/person/year).

Italian children were the most exposed to antibiotic therapy (weighted average prevalence 47.9%) and UK children the least (14.2%) (Figure 4). Furthermore, Italian and Canadian children treated with an antibiotic received, respectively, 2.1 and 2.2 prescriptions each, compared to Dutch children, who received 1.4 each.

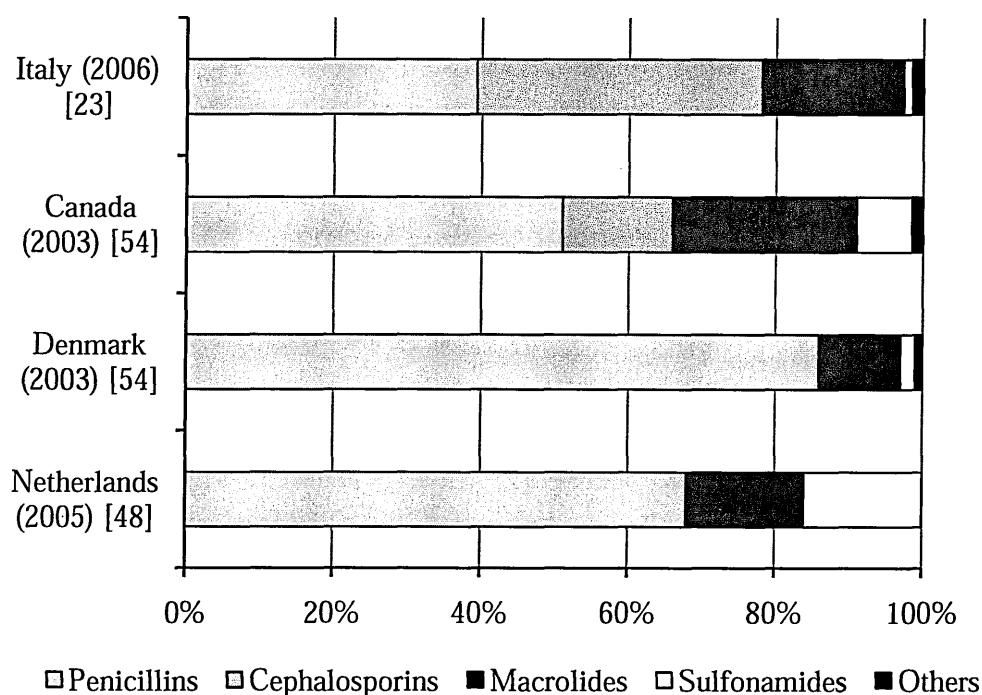
**Figure 4 – Prevalence (%) of antibiotic drug prescription**



**4. Inter-country variation in antibiotic choice.**

Data concerning the distribution of prescriptions by antibiotic class were reported for Italy, the Netherlands, Canada and Denmark.<sup>23,44,45,48,49,55</sup> Penicillins were the most prescribed antibiotics and represented from 39% in Italy to 89% in Denmark of antibiotic prescriptions (Figure 5). Cephalosporins were the second class in Italy (39% of prescriptions) and the third in Canada (15%), while they are hardly prescribed in the Netherlands and in Denmark. Macrolides covered from 11% in Denmark to 25% in Canada of antibiotic prescriptions.

**Figure 5 - Percentage distribution of antibiotic prescriptions by class**



Only a few studies reported the most frequently prescribed antibiotics, with data from Italy, the Netherlands and Canada.<sup>23,36,50</sup> Four drugs (amoxicillin+clavulanic acid, amoxicillin, clarithromycin and azithromycin) were among the 10 leading drugs in all three countries. A total of 14 drugs covered the 10 most used antibiotics in the countries considered representing 94% of total antibiotic prescriptions in Italy and the Netherlands. Amoxicillin was the leading drug in the Netherlands and Canada, while amoxicillin plus clavulanate the most prescribed in Italy. On the other hand, the combination of amoxicillin and clavulanate was infrequently used in Canada. Clarithromycin and azithromycin were both widely used everywhere, but in variable amounts in each country analysed (Table 4). Finally, the use of some antibiotics is limited to, and is a peculiarity of, single countries: cefaclor is widely prescribed in Italy and Canada, while it is rarely prescribed at all in the Netherlands. Pheneticillin, an oral narrow-spectrum penicillin, is prescribed only in the Netherlands, ceftriaxone only in Italy, gentamycin and cephalixin only in Canada.

Table 4 - The 10 most frequently prescribed antibiotics in Canada, the Netherlands and Italy

Canada			Netherlands			Italy		
(2001) <sup>36</sup>			(2005) <sup>50</sup>			(2006) <sup>23</sup>		
Drug	Treated		Drug	Prescriptions		Drug	Treated	Prescriptions
	%			%			%	%
Amoxicillin	45.3		Amoxicillin	43.2		Co-amoxiclav	45.0	30.1
Clarithromycin	12.4		Clarithromycin	10.4		Amoxicillin	26.8	16.7
Cefaclor	10.2		Co-amoxiclav	10.4		Clarithromycin	21.7	10.5
Cotrimoxazol	9.6		Azithromycin	5.4		Azithromycin	16.7	8.1
Azithromycin	8.9		Pheneticillin	5.2		Cefaclor	12.9	7.8
Cefprozil	7.5		Trimethoprim	4.4		Cefixime	12.3	6.1
Co-amoxiclav	5.3		Cotrimoxazol	4.4		Ceftriaxone	3.0	5.5
Gentamycin	5.1		Nitrofurantoin	4.3		Ceftibuten	8.1	4.0
Penicillin V	5.1		Doxycyclin	3.6		Cefpodoxime	6.3	3.7
Cephalexin	4.2		Flucloxacillin	2.3		Cefuroxime	1.9	1.1

## **D. ANTI-ASTHMATIC DRUG PRESCRIPTIONS**

### **1. Search results**

A total of 156 articles were retrieved from the literature databases: 80 from Medline, 76 from EMBASE and 16 from each database. In all, 144 papers were excluded because they were specific to a single anti-asthmatic drug, or a single anti-asthmatic drug subclass, or analysed only the quality of prescriptions. After the identification of 4 additional studies through a manual search of the references, a total of 16 pharmacoepidemiological studies fitted the inclusion criteria (Table 5).

### **2. Characteristics of the studies**

All studies involved preschool and school age children. A total of six countries were involved in these 16 studies: Italy (5 studies), the Netherlands (3 studies), Norway, Denmark, Canada (2 studies each) and USA (1 study). The data sources were mainly regional/multiregional/national prescription databases or pharmacy dispensing databases (9 articles), followed by health insurance database (3 articles), physicians (2) and questionnaires (1). Eleven surveys evaluated only anti-asthmatics, and five included all drug prescriptions (Table 5). A wide heterogeneity was found between studies with regard to sample size (from a minimum of 6,417 to a maximum of 4,259,103 subjects).

Only nine studies were comparable in terms of data source and age and were thus selected for the meta-analysis (Figure 6).



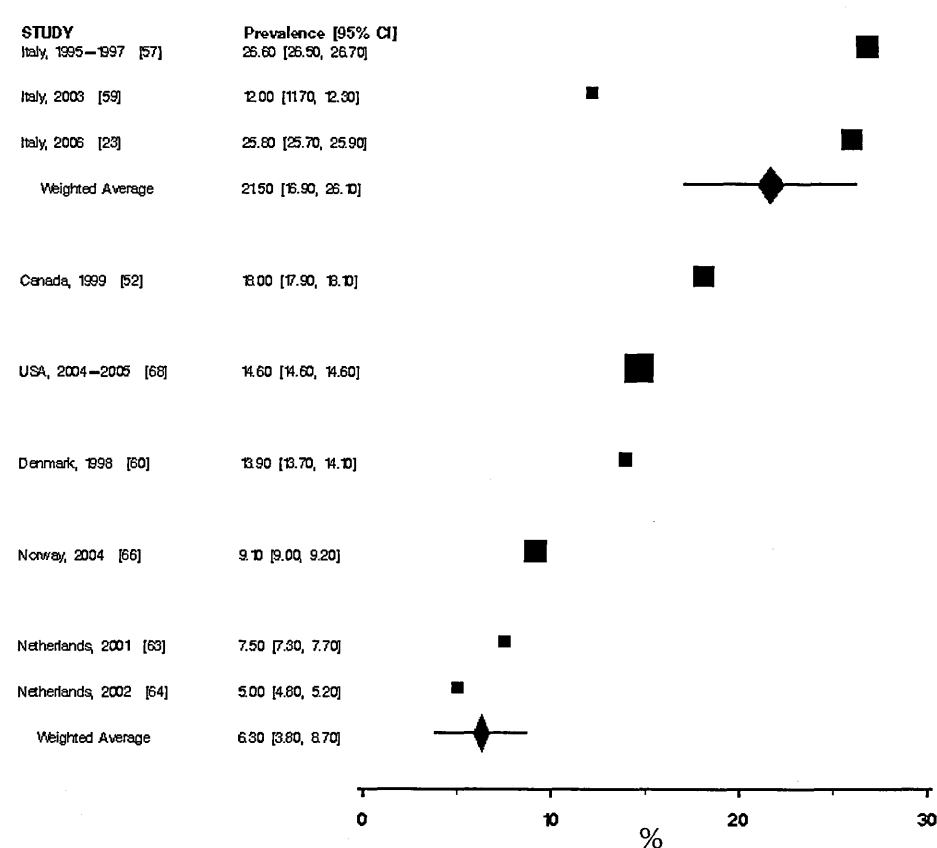
Table 5. Characteristic of the studies evaluating anti-asthmatic drug prescriptions

Ref.	Period	Country	Population (n)	Age (years)	Source of prescription data	Prevalence rate (%)
57	1995-1997	Italy	1,254,958	≤15	Prescription DB	26.6
29*	1998	Italy	6,417	≤12	Paediatricians	20.7
58	2000	Italy	417,559	≤14	Prescription DB	22.2
59	2003	Italy	55,242	≤17	Prescription DB	12.0
23*	2006	Italy	923,353	≤14	Prescription DB	26.0
60	1998	Denmark	139,727	≤15	Prescription DB	13.9
61	2002	Denmark	125,907	6-14	Prescription DB	7.7
62*	1998	Netherlands	25,020	≤16	Pharmacy dispensing DB	7.4
63	2001	Netherlands	74,580	≤17	GPs	7.5
64	2002	Netherlands	72,240	≤14	Pharmacy dispensing DB	5.0

65*	2000-2002	Norway	11,708	15	Questionnaires	6.5
66	2004	Norway	1,192,841	≤19	Prescription DB	9.1
67	1995	Canada	174,198	5-15	Insurance plans DB	17.0
36*	1999	Canada	1,031,731	≤17	Insurance plans DB	18.0
68	2004-2005	USA	4,259,103	≤17	Insurance plans DB	14.6

\* studies evaluating all drug prescriptions

**Figure 6 - Prevalence (%) of anti asthmatic drug prescriptions in children and adolescents ( $\leq 18$  years)**



### 3. Inter-country variation in prevalence rate.

Differences in anti asthmatic use emerged among the 6 countries considered, both quantitatively (Figure 6) and qualitatively.

In general, two prescribing patterns can be identified, with some countries with high anti asthmatic prescribing levels (Italy, Canada and USA), with prevalence ranging from 17 to 26.6% and countries with low anti asthmatic prescribing levels (Norway and the Netherlands), with prevalence ranging from 5 to 9.1% . Italian children were the most exposed to anti asthmatic therapy (weighted average prevalence 21.5%) and Dutch children the least (weighted average prevalence 6.6%).

Six out of nine studies reported that the prevalence of anti-asthmatic drug prescriptions was higher in boys than in girls (male/female ratio  $\approx 1.2$ ) and two articles reported that after age 15 these sex differences disappeared or even girls rate surpassed boy rate. The prescription prevalence by age, reported by the majority of the studies, decreased from 1 year old children to adolescence, with the exception of one study that reported an increase from 0-2 years old children to 6 years old and then a decrease from 6 to adolescence.

#### **4. Inter-country variation in choice of anti asthmatic treatment.**

Data concerning the distribution of prescriptions by anti asthmatic class were reported for Italy, Denmark, the Netherlands, Canada, and the USA. In Italy inhaled steroids were the most frequently prescribed class and covered 60% of anti-asthmatic prescriptions and 86% of the treated children, while short acting  $\beta_2$  agonist were the most prescribed in the other countries, covering a percentage of anti-asthmatic users ranging from 58% in the USA to 93% in Denmark.

The most frequently prescribed anti asthmatic drugs were available only for three countries. These drugs are beclometasone and salbutamol in Italy, salbutamol and fluticasone in Canada, salbutamol and montelukast in the USA. In Italy, both beclometasone and salbutamol are prescribed mainly as nebulised suspension.

## **E. ANTIDEPRESSANT DRUG PRESCRIPTIONS**

### **1. Search results**

A total of 115 articles were retrieved from the literature databases: 60 from EMBASE and 49 from Medline, and 6 from both. In all, 104 papers were excluded.

### **2. Characteristic of the studies**

A total of 12 studies reported the antidepressant prevalence (Table 6).<sup>69-79</sup> The studies concerned 8 countries: three studies involved the Netherlands<sup>77-79</sup>, two Italy,<sup>70,75</sup> Germany<sup>71,79</sup>, France,<sup>72,80</sup> and the UK<sup>73,74</sup>, and one Denmark,<sup>79</sup> Ireland<sup>69</sup> and Spain.<sup>76</sup> One paper compared data collected in different countries.<sup>79</sup> Eight studies were published after 2005 and six reported data concerning the period 2003-2005, 4 of which also reported the prevalence trend across years,<sup>71,74,80,81</sup> while one compared the 2005 versus 2001 prevalence.<sup>78</sup>

Four studies reported data on other psychotropic drug classes<sup>70,72,75,77</sup>, while one concerned only SSRIs and selective norepinephrine reuptake inhibitor (SNRI) prescriptions.<sup>76</sup>

Most of the studies involved children and adolescents, even if with different upper limits of age; 5 of 12, in particular, involved patients less than 20 years old. One study was focused on adolescents only and was therefore not taken into account in the analysis.<sup>72</sup>

The sample size varied widely and ranged between 37,650 and 1,500,000.

### **3. Inter-country variation in prevalence**

Wide differences were found in the prevalence depending on the country and the observation period. When taking into account the most recent data for each country, the results showed higher prevalence in the United Kingdom (5.7 per 1,000)<sup>74</sup> and a lower prevalence was reported in Denmark (1.8 per 1,000)<sup>79</sup>.

**Table 6 – Characteristics of the studies evaluating antidepressant use in children and adolescents**

<b>Ref.</b>	<b>Country</b>	<b>Year</b>	<b>Age (years)</b>	<b>N. children</b>	<b>Prevalence (‰)</b>	<b>F/M</b>
77	Netherlands	1999	0-19	37,670	4.4	-
79	Denmark	2000	0-19	111,452	1.8	1.72
79	Germany	2000	0-19	480,680	1.1	1.16
79	Netherlands	2000	0-19	72,570	5.4	1.03
73	UK	2001	0-18	-	7.1	-
75	Italy	2001	0-18	1,500,000	2.8	1.45
72	France	2002	13-17	120,908	7.7	1.86
69	Ireland	2003	0-15	250,930	4.3	-
80	France	2003	0-17	6,534	3.7	-
71	Germany	2003	0-19	279,083	3.4	2.00
70	Italy	2004	0-17	1,484,770	2.4	1.20
74	UK	2004	0-18	-	5.7	-
76	Spain	2004-05	0-18	919,051	4.8	1.22
78	Netherlands	2005	0-17	62,969	2.0	-

Prevalence was higher in females than in males, with a female/male ratio ranging between 1.03 and 2.00. The distribution of prevalence by age group was reported by six studies: the prevalence increased with increasing age and was higher in the adolescents, ranging from 4.5 in the Netherlands to 15 per 1,000 in France.<sup>70,71,73,78-80</sup>

Only three studies reported the most prescribed antidepressants in order of prevalence: hypericum was the most prescribed drug in Germany, sertraline in Italy, and fluoxetine in Spain (Table 7).<sup>70,71,76</sup>

**Table 7 – Most prescribed antidepressants in Germany, Italy, and Spain.**

Germany (2003) <sup>71</sup>		Italy (2004) <sup>70</sup>		Spain (2005) <sup>76 *</sup>	
Drug	Prevalence (‰)	Drug	Prevalence (‰)	Drug	Prevalence (‰)
Hypericum	1.51	Sertraline	0.52	Fluoxetine	1.49
Opipranol	0.40	Paroxetine	0.49	Sertraline	1.23
Imipramine	0.33	Citalopram	0.38	Paroxetine	0.69
Doxepine	0.30	Fluoxetine	0.23	Citalopram	0.39
Amitryptiline	0.29	Amitryptiline	0.18	Mirtazapine	0.31
Citalopram	0.23	Trazodone	0.17	Venlafaxine	0.29
Fluoxetine	0.18	Escitalopram	0.16	Escitalopram	0.19
Sertraline	0.16	Venlafaxine	0.14	Fluvoxamine	0.16

\*SSRIs and SNRIs only.

The SSRI and venlafaxine prescription prevalence in Spain was 2.8 fold higher than in Italy (4.8 versus 1.7 per 1,000). This ratio changed depending on the drug: it was

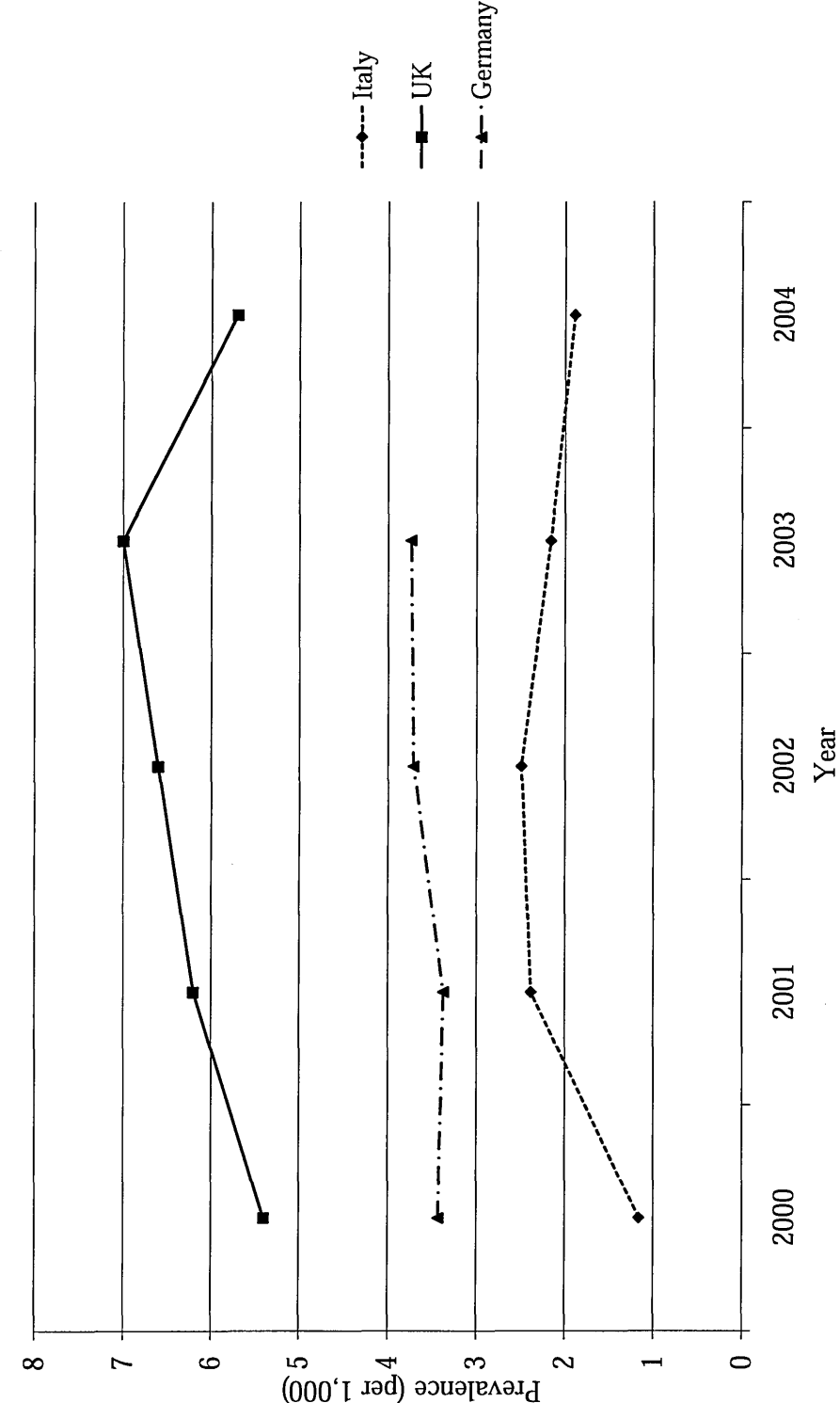
highest for fluoxetine (6.5), while the prevalence of citalopram and escitalopram were nearly the same in the two countries.

Figure 7 reports the trend of antidepressant prevalence in the UK, Germany and Italy. The area under the prevalence-time curve (AUC) from 2000 to 2003, calculated according to the linear trapezoidal rule, was 3-fold and 2-fold higher in the UK than in Italy and Germany, respectively.

In spite of the different rates, between 2000-2003 the prevalence increased by 80% in Italy and by 30% in the United Kingdom, while a less significant increase was observed in Germany (9%). This trend was mainly related to an increase in SSRI prescriptions, consisting of 240% in Italy and 147% in Germany. A slight decrease in prevalence of antidepressant prescriptions was also reported in the Netherlands: from 2.3 per 1,000 in 2001 to 2.0 per 1,000 in 2005.<sup>3</sup>



Figure 7 – Trend of antidepressant prevalence, 2000-2004



## **F. DISCUSSION**

The increased attention towards the evaluation of drug use in children suggests that there may be recent interest in closing the gap in this area. However, most of the studies, especially those published since 2000, focused on one drug class only. In particular, nearly half of the studies concerned psychotropic drugs. This is probably due to the on-going debate regarding the safety and efficacy of psychotropic drugs in the paediatric population and to the concerns associated with the increased use of these drugs.<sup>82,83</sup> Moreover, 30% of the studies concerned antibiotics. This can be explained by the fact that they are the most frequently prescribed drugs, and are often given in an inappropriate manner, increasing the risk of bacterial resistance.<sup>84</sup> On the contrary, some drug classes were not monitored. Only four studies looked at anticonvulsant use, while gastrointestinal drugs, commonly used in infants, were studied in only one study.

Most studies were from Europe and North America, with only nine studies from developing countries. This imbalance could be due to several reasons, in particular the fact that this review is focused only on outpatient drug prescriptions, a setting characteristic of developed health systems. In addition, the difficulty in collecting reliable data and in publishing papers should be considered. However, despite the fact that most studies were from the North, qualitative drug utilization profiles underline different therapeutic needs (e.g. antimalarials versus respiratory drugs) and suggest that different priorities exist between children living in the South and the North of the world.

### **1. Methodological considerations**

A wide heterogeneity of studies was found, with large differences in study types (design and methods), populations (in terms of sample size and age groups), and data collected, making a comparative evaluation often difficult or incomplete.

Use of different data sources contributes to this heterogeneity. Every source has strengths and limitations that should be taken into account in planning and evaluating drug utilization studies.

Prescription databases have the advantage of monitoring the prescriptions dispensed by all the physicians to an entire population in a specific region or nation. The main limits are that over the counter drugs and drugs not reimbursed by the national health service are not included, that the therapeutic indication is often lacking, and that it is not possible to know if the patient actually took the drug.

On the other hand, the advantages with data collected by general practitioners and paediatricians are that also drugs that are not reimbursed can be monitored and that, in many cases, details about the disease for which a drug was prescribed can be collected. The limits with this type of data collection is that the number of physicians involved is often limited and that it is only possible to collect information about children actually visiting physicians. It is not therefore possible to estimate the drug prescription prevalence in the population and to know if the patient filled the prescription and took the drug.

Surveys using questionnaires administered to patients or parents can monitor the actual use of drugs. However, only a sample of the population can be surveyed and only for a short period of time (usually a few weeks). Recall bias is possible and reliability of information is scarce.

Thus, the overall accuracy of these data sources can affect the estimates. However, the heterogeneity of the studies is not explained only by the different data sources.

If only studies that analyzed all drug prescriptions are considered, nearly half are found to concern specific age groups. Moreover, also the 11 studies that covered the entire paediatric population used different age ranges, leaving 4 studies comparable on the basis of data source and children's age.

Moreover, the sample selected in each drug utilization study may not be representative of the national paediatric population, and this contribute to increase the difficulty in comparing different prescribing profiles.

Considering the four studies comparable on the basis of data source and children's age, the percentage of national paediatric population covered by each sample ranged between nearly 1% in the Netherlands and 14% in Italy. The prescribing pattern observed in a specific regional setting (e.g. Greenland), may be different from other regions in the same country.

Only 6 studies reported the prevalence trend by age, while the most frequently prescribed drugs were reported in only 4 studies (and in two cases without reporting the prevalence). An improvement in the methodology of drug utilization studies is therefore needed in order to collect data that can be compared with other regional or national settings. In this regard, it is interesting to note that differences in data sources children's age were found also in a multinational cohort study that compared prescribing profile in the Netherlands, UK, and Italy.<sup>32</sup>

## **2. Differences in drug prescribing to children and adolescents**

Despite the limitations highlighted above, quantitative and qualitative differences in prescribing patterns to children were found. Prevalence of drug prescription in developed countries varied between 51 and 70% and each child treated received, on average, between 1.3 and 5.3 prescriptions.

On the basis of the results of the meta-analysis it can be estimated that 60% of children receive an average of three drug prescriptions in a one year period. In particular, 33% of children receive antibiotics and 15% receive anti-asthmatics.

However, while for the majority of the studies the prevalence was nearly 60%, some differences were found when evaluating the prevalence of the most frequently prescribed drug classes.

In fact, a wide inter-country variability (quantitative and qualitative) was found for antibiotic, anti-asthmatic and antidepressant drug prescriptions, with the identification of regional clusters in drug consumption, especially for European countries. These are well-acknowledged data and are largely observed also in the general population, both in the community and hospital settings.<sup>85,86</sup>

Italy, along with Canada, had the highest paediatric antibiotic and anti-asthmatic prescription rates, and, contrarily, northern EU countries (the Netherlands and UK) had significantly lower rates.

It was interesting to note, for example, that Italian children have a threefold greater chance of receiving an antibiotic or an anti-asthmatic compared with children living in the Netherlands, even if the all drug prescription prevalence in the two countries were the same.

A different profile emerged when analyzing antidepressant drug prescription, with a greater prevalence in the UK compared with other European countries.

The differences in drug prescription prevalence appear not to be related to the prevalence of the diseases. For example, the prevalence of asthma symptoms in children

was similar in Italy and in the Netherlands (8.4 and 7.3%, respectively)<sup>87,88</sup>, despite the different prevalence of anti-asthmatic drug prescriptions.

Antidepressants were used twice as often in the UK than in Germany, even though the number of Disability Adjusted Life Years (DALYs) per 1,000 attributable to neuropsychiatric disorders is the same in the two countries (6.8). The antidepressant prevalence in Spain ranked second, despite the value of DALYs attributable to neuropsychiatric disorders (5.4 per 1,000) was the lowest among the countries surveyed in this review.<sup>89</sup>

Some differences also emerged in the quality of drug prescribing. For example, penicillins, usually recommended as first-line therapy for most common paediatric respiratory infections,<sup>90-93</sup> were the most frequently used class of antibiotics in children everywhere. They were, however, twice as likely to be prescribed by Danish and Dutch GPs than Italian GPs. Cephalosporins, a second-line therapy in most common paediatric respiratory infections (non type I allergy to penicillin; treatment failure with antibacterial agent and/or presence of severe symptoms), are widely used in Italy and Canada while, on the contrary, they are practically never prescribed in Denmark and in the Netherlands (representing less than 1% of total paediatric antibiotic prescriptions).

A different profile emerged also for anti-asthmatic class prescriptions: for example, inhaled steroids were commonly used in Italy and were prescribed to 86% of anti-asthmatic users.

Despite few studies reporting the most frequently prescribed drugs, it is interesting to note that for paracetamol and salbutamol there is a similarity in prescribing habits

between countries whereas for other drugs differences are wide, suggesting different drug policies, as well as different physician attitudes in prescribing drugs.

The same peculiarities can be found analysing the most frequently prescribed antibiotics. Amoxicillin and amoxicillin plus clavulanate (drugs of choice in most paediatric infections) were the most frequently prescribed drugs everywhere, although in different amounts.

Other antibiotics were more commonly prescribed in one country: pheneticillin in the Netherlands, sulphamethoxazole and trimetoprim in Canada, cefaclor in Italy and Canada.

The presence of ceftriaxone (a third generation cephalosporin by parental administration only) as the fifth most commonly used antibiotic in Italy is of particular concern. A total of 6.5% of all outpatient Italian children treated with antibacterial received parental antibiotics; in Canada, this figure is less than 1%.

Geographical differences in drug use depend to a large degree on the existing healthcare systems, which influence drug regulation and the national pharmaceutical market structure's, rather than on socio-cultural and economic determinants, some of which are related to physicians (i.e. diagnostic uncertainty, especially for the youngest, or differences in diagnostic labelling, time or market pressure), and others on patients/parents (i.e. patient's general condition, or socio-economic status).

The main aims of the project were:

1. To evaluate the prevalence of drug prescriptions in a large Italian out-patient paediatric population
2. To compare the prescribing patterns in different settings, at different levels (multinational, national, regional, local)
3. To monitor drug prescription patterns and the appropriateness of therapies by evaluating their adherence to international treatment guidelines
4. To estimate the prevalence and the quality of care of chronic diseases (e.g. asthma) using drugs as indirect indices
5. To monitor drug prescription trends over several years and also evaluate the impact of statements issued by drug regulatory agencies



## **VI. METHODS**

## **A.THE ITALIAN HEALTH SYSTEM FRAMEWORK**

Italian health care is provided free or at a nominal charge through a network of 195 local health units (LHUs) covering an average of 290,000 citizens. Every Italian resident is registered with a family (paediatric or general) practitioner. There are about 7,450 primary care paediatricians caring for over 7 million children, the majority of whom are less than 6 years old. Children are assigned to a paediatrician until they are 6 years old; afterwards, the parents can choose to remain with the paediatrician until the child is 14 years old or to register the child with a general practitioner. All adolescents over 14 years of age are assigned to a general practitioner.

A national formulary is available in which drugs are categorised into 2 classes: class A includes essential drugs that patients do not have to pay for and class C contains drugs not covered by the National Health Service. Some drugs are reimbursed for some indications only. Most antibiotics and nearly all chronic disease therapies are free of charge.

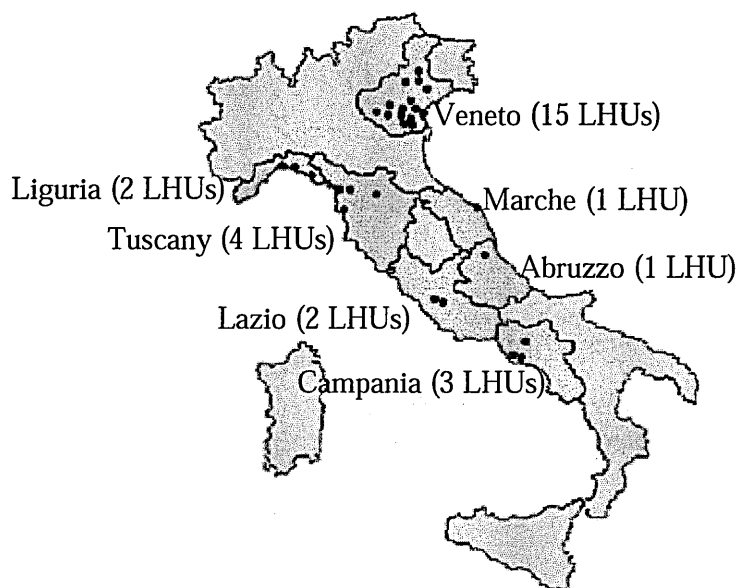
## **B. DATA SOURCES:**

### **1. The ARNO database**

The ARNO database is a population oriented database that collects information on drug use outside the hospital setting in Italy. The system, active since 1988, is run by CINECA, a National Interuniversity Consortium, and merges information regarding prescriptions, the population, geographical areas, and the community setting into a single database. A total of 29 local health units, located in 7 Italian regions from northern, central and southern areas, and representative of urban and rural settings, were part of the ARNO project at December 2008

(<http://osservatorioarno.cineca.org/arnoeng.htm>), representing a population of 10 million inhabitants (Figure 8).

**Figure 8 - Geographical distribution of the LHUs participating to the ARNO project.**



Each LHU joined the ARNO network on a voluntary basis. A data quality check was performed before adding each LHU dataset to the data warehouse. Datasets with missing or incorrect data greater than 10% of the total records were excluded.

When joining the ARNO project, each LHU general director provided the authorisation to analyse the prescription data using a unique anonymous patient code and to use data for scientific publication.

## **2. The Lombardy Region administrative prescription database.**

This is a database routinely updated for administrative and reimbursement reasons. The database stores all community (i.e. outside hospital) prescriptions, reimbursed by the National Health Service (NHS), issued to individuals living in Lombardy Region, in northern Italy. The Italian system works in such a way that outpatients receive prescriptions from paediatricians, GPs, or other specialists and then get the medicines

free of charge from retail pharmacies. Outpatients receiving prescriptions in the private sector get the medicines free of charge through GP prescriptions. Each local pharmacy provides these prescriptions to the Regional Health Authority to get reimbursed. The Regional Health Authority electronically stores these prescriptions into the regional administrative database. In this system, a unique patient code prevents double counting of individuals who have been prescribed drugs by more than one physician.

The regional administrative database also collects the hospital discharge forms, besides the prescription data. Using the patient code it was possible to link the information concerning drug prescriptions with those regarding hospital admissions.

### **3. Strengths and limitations**

Prescription databases have the advantage of monitoring the prescriptions dispensed by all the physicians to an entire population in a specific region or nation. Moreover, ARNO database collects data concerning a long time period (even if only for a limited number of LHUs) and this can allow a monitoring of the prescribing pattern across time. The main limits are that over-the-counter drugs and drugs not reimbursed by the national health service are not included (e.g. paracetamol, ibuprofen, antiemetic drugs), that the therapeutic indication is lacking, and that it is not possible to know if the patient actually took the drug. Moreover, information concerning the socio-economic status or the educational level of the individuals are not available.

The fact that participation to the ARNO network is on voluntary basis may have created a kind of “selection bias” and LHUs may not be fully representative of the Italian situation. However, ARNO is the only multi-regional prescription database existing in Italy and cover 17% of the national population. Moreover, LHUs joining this network are representative of urban and rural setting.

#### 4. Synopsis of the characteristics of the studies

Observation period and the study population varied depending on the different studies.

Table 8 summarises the main indicators (source, setting, age group, sample size) of the studies presented in this thesis.

**Table 8- Characteristics of the drug utilization studies presented in the thesis**

Chapter	Drug	Year	Source	Setting	Age (ys)	Sample size
VII.B	All	2006	ARNO	Italy (22 LHUs)	<14	923,353
VII.C	All	2005	Lombardy	Lombardy	<18	1,543,203
VII.D	All	2005	Lombardy	Milan	<18	122,714
VIII.A	Psychotropics	2004	ARNO	Italy (27 LHUs)	<18	1,484,770
VIII.B	Anti- asthmatics	2003	Lombardy	Lecco LHU	<18	55,242
IX.B	All	2005	Lombardy	Lombardy	<14	923,177
IX.C	All	2005	Lombardy	Lombardy	6-13	548,922

Differences in the sample chosen were due to different reasons, in part contingent (e.g. the availability of the data during the PhD project period), and in part due to the pattern of drug use. For example, in evaluating the pattern of anti-asthmatic or psychotropic drug prescriptions adolescents should also have been included.

The most recent available data were analysed when performing each study.

Studies reported in the chapter VII were firstly performed using 2003 data<sup>94</sup> and then the analyses were subsequently updated using the most recent available data for each database (2006 for the ARNO database and 2005 for the Lombardy region database).

### **C. STATISTICAL ANALYSIS**

Prescribed drugs were classified according to the International Anatomic-Therapeutical-Chemical Classification system (ATC).

Data were managed and analysed using an anonymous patient code. Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group. Incidence was defined as the number of people who received a drug for the first time by the total number of residents. In order to evaluate pharmaceutical consumption, the number of packages of medications (boxes) was used as an indicator of the whole drug exposure during the considered period. In fact, it can be related to the same medicine prescribed repeatedly or to different medicines.

A Mantel-Haentzel  $\chi^2$  test was performed in order to compare the drug prescription prevalence in boys and girls.

The rate of hospitalisation was estimated considering hospital discharge forms, by dividing the number of patients <18 years old hospitalised at least once during the observation period by the total number of residents < 18 years old.

The relationship between the prevalence of the most prescribed therapeutic classes and between the prevalence in the paediatric and adult population by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

The relationship between the prevalence and hospitalisation rates by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

A stepwise multivariate logistic regression analysis was performed to evaluate the association between drug prescription and age, gender, LHU of residence, kind of physician who is in charge of the patient (paediatrician, general practitioner) and physician gender.

In the study concerning anti-asthmatic drug prescriptions (chapter VIII.B) a multinomial regression analysis was performed, since the dependent variable was the degree of exposure to anti-asthmatic drugs, which was classified into three categories: occasional (one package/year), low (2-3 packages/year) and high use ( $\geq 4$  packages/year).

More details concerning the statistical analyses will be provided in each chapter.

The results of the statistical analysis will be reported in this manner: test used; degree of freedom (d.f.); p-value.

Statistical analysis was performed using SPSS 10.1 software, IBM DB2 Intelligent Miner for Data version 6 and SAS software, version 9.1. WinNonLin version 4.1 was used in calculating AUC.

A P value  $< 0.05$  was considered statistically significant.

## **VII. A COMPARISON BETWEEN DIFFERENT ITALIAN SETTINGS**



## **A. INTRODUCTION**

The analysis of drug utilization studies presented in the review of the literature highlighted that quantitative and qualitative differences between countries in drug prescription to children and adolescents exist.

Differences in drug consumption in the overall population were found also at the Italian regional level,<sup>95,96</sup> but no data are available regarding the paediatric population.

In this regard, the differences in the profile of drug prescription to children and adolescents were investigated at different levels (national, regional and local). The results of these studies will be presented below and will be discussed at the end of this chapter.

## **B. DIFFERENCES BETWEEN ITALIAN REGIONS**

### **1. Aim of the study**

The aims of the study were to describe the prescribing pattern in the Italian paediatric population, to compare the drug prescription prevalence between local health units located in different geographic areas and to analyze the prevalence trend across years.

### **2. Methods**

The analysis involved all paediatric prescriptions reimbursed by the National Health Service and dispensed by the retail pharmacies of 22 Italian LHUs in 6 Italian regions (Veneto, 13 LHUs; Liguria, 2 LHUs; Tuscany, 4 LHUs; Abruzzo, 1 LHU; Lazio, 1 LHU; Campania, 1 LHU) which were part of the ARNO project between 1 January 2006 and 31 December 2006.

The study population was composed of 923,353 children under 14 years of age living in the above LHUs. The study sample represented 14% of the Italian paediatric population and the male/female ratio was 1.06. The gender and age distribution of the sample was not different from that of the Italian paediatric population.

The trend of annual prevalence of drug prescription in the 2000-2006 year period was evaluated in a subset of 20 LHUs for which the data were available for all the years.

The prescribed drugs were classified according to the International Anatomical Therapeutic Classification system (ATC).

The number of medication packages was used as an indicator to evaluate the pharmaceutical consumption.

Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group. A Mantel-Haentzel  $\chi^2$  test was performed to compare the drug prescription prevalence in boys and girls.

The area under the prevalence-time curve (AUC) from time 0 to 14 years (data plotted at the mid-time interval) were calculated according to the linear trapezoidal rule and compared by the paired t-test. The decreasing phases of the prevalence versus time curve were estimated by log-linear least square fitting of the 3- and 13-year age points. Comparisons were made using the t-test.

The relation between the prevalence of the most prescribed therapeutic classes by LHU was investigated using the non-parametric Spearman rank correlation test.

Statistical analysis was performed using SPSS 10.1 software and IBM DB2 Intelligent Miner for Data version 6. Win Nonlin version 4.1 was used in calculating the AUC.

A p-value <0.05 was considered to be statistically significant.

### 3. Results

#### *a) Drug prescribing pattern in Italy*

During 2006, 561,237 children (61% of the population) received at least one drug prescription. The highest prevalence was observed in the 1-4 year old period (average value 76%), it then decreased according to a two phase slope: the 4-7 year old (76 to 58%) faster than the 7-13 year old period (58 to 43%) (Figure 9).

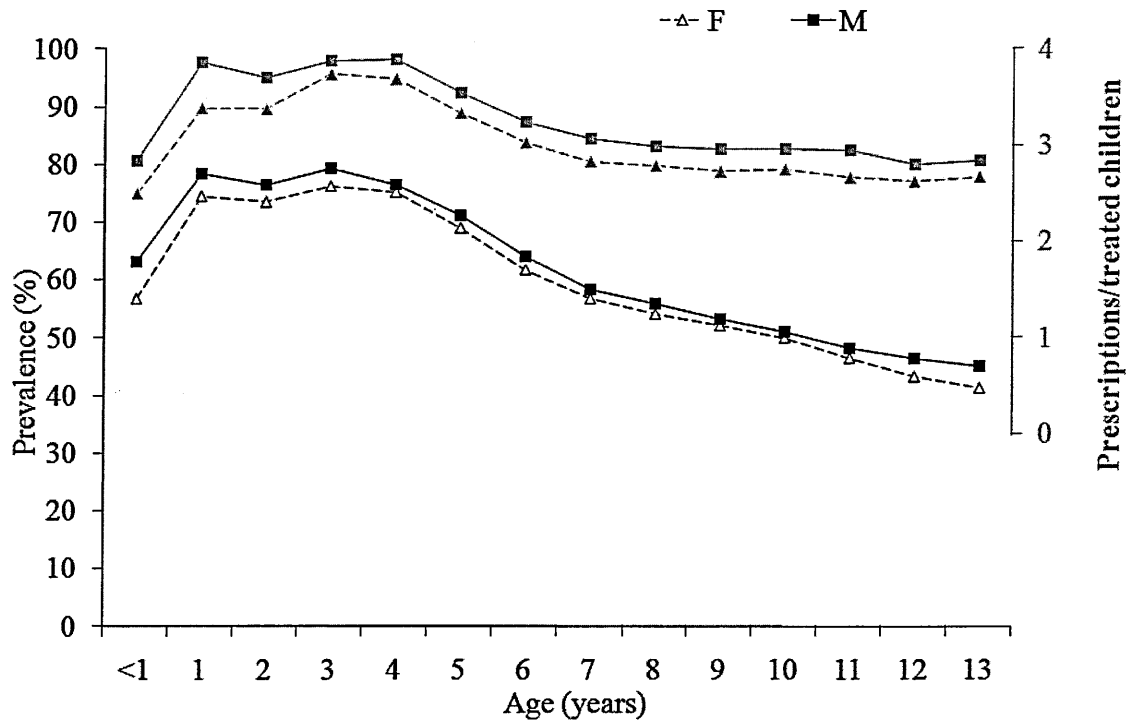
Prevalence was slightly higher in boys than girls for all ages ( $\chi^2 = 655$ ; d.f.=1  $p < 0.001$ ), but had the same profile. The AUC<sub>0-14</sub> male/female ratio was 1.04.

In all, 1,117 paediatricians prescribed drugs to 77% of the children, while to 19% of the children drugs were prescribed by 5,871 general practitioners. A total of 1,805,521 prescriptions were dispensed, corresponding to 2,697,979 packages. Each treated child received a median of 3.2 prescriptions (median 3) and 4.8 packages (median 3) during the one year study period. Boys received a greater average number of prescriptions (3.3 versus 3.1) and packages (5.0 versus 4.6) than girls.

The highest number of prescriptions/treated child was observed in children 3-4 year old (3.8; median 3). While prescription prevalence decreased steadily in the 7-13 year old period, the decrease in average number of prescriptions per treated child was less prominent.

A total of 22% of treated children received only one package, while 27% received more than 5 packages (and 10 or more packages were dispensed to 11%). The rate of children receiving six or more packages was higher in males than females (28 versus 25%;  $\chi^2 = 862$ ; d.f.=1;  $p < 0.001$ ), and in children 1-4 years old (33%) compared to those <1 year (18%) and  $\geq 5$  years (23%) ( $\chi^2 = 31,920$ ; d.f.=2;  $p < 0.001$ ).

**Figure 9- Prescription prevalence and average number of prescriptions/treated child by gender and age**



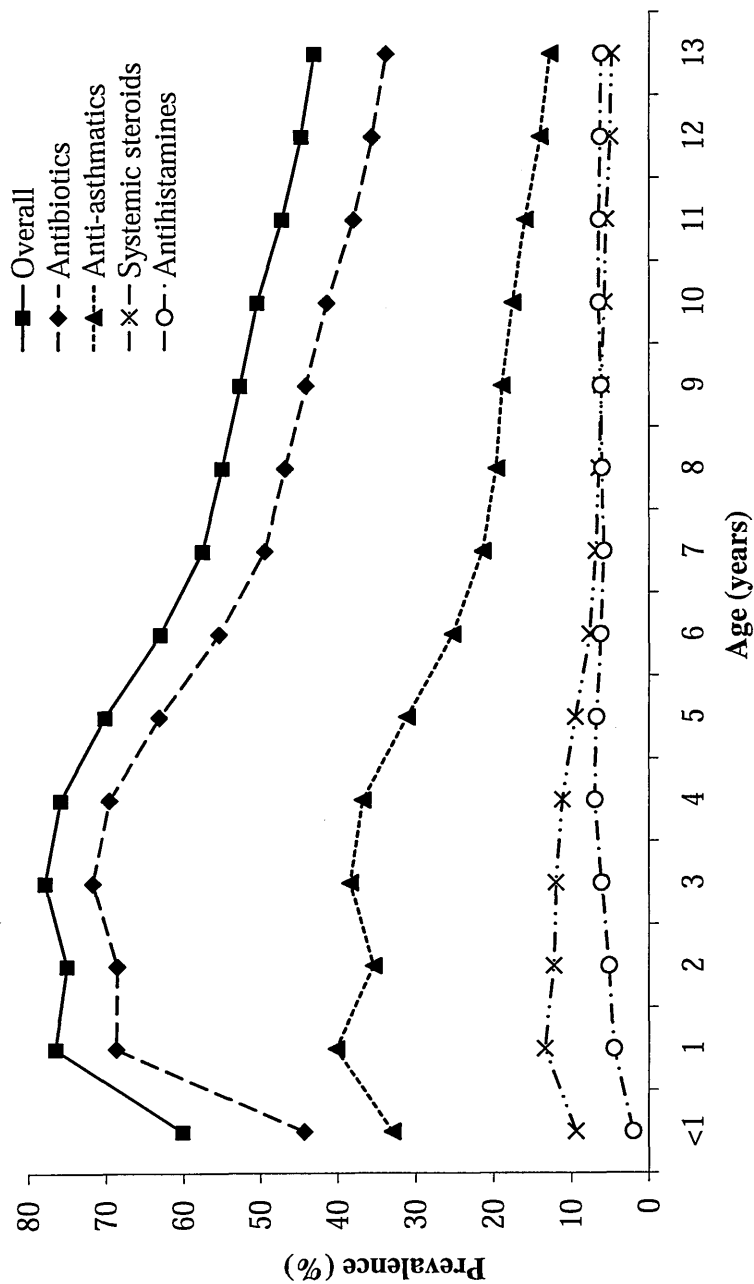
Antibiotics were the most prescribed therapeutic class (52% of the population), followed by anti-asthmatics (26%), systemic corticosteroids (8%), and antihistamines (6%). Altogether, these four therapeutic classes comprised 90% of prescribed packages. Most children received drugs belonging to one therapeutic class only (52% of treated children), while 32% received drugs belonging to two classes (mainly antibiotics and anti-asthmatics, prescribed to 26% of treated children), and 16% to 3 or more classes (8% received antibiotics, anti-asthmatics and systemic steroids).

Figure 10 reports the prevalence trend by gender and age of the four most prescribed therapeutic classes. The trend for antibiotics is similar to the overall trend, while the highest value of anti-asthmatic and systemic steroid prevalence was observed at 1 year (40 and 13%, respectively). The prevalence of anti-asthmatics reached a second age-

dependent peak at 3 years (39%), while the systemic steroid prevalence progressively decreased after 1 year.

The prevalence of anti-histamines increased with increasing age, reaching a maximum of 7% at 4 years, then slightly decreased.

Figure 10 - Prescription prevalence by age of the four most prescribed therapeutic classes.



The AUC<sub>0-14</sub> male/female ratio ranged between 1.03 for the antibiotics and 1.30 for the anti-histamines.

Among the most prescribed therapeutic classes, antibiotics were associated with the highest average number of packages per treated child (3.2), while systemic steroids with the lowest (1.7). The greatest proportion of children receiving more than 5 packages was observed among antibiotic users (14%), followed by anti-asthmatic users (9%). On the contrary, 65% of children treated with systemic steroids received only one package, compared to 54% of those treated with anti-histamines, 43% of those treated with anti-asthmatics, and 31% of children treated with antibiotics.

Penicillins were the most prescribed antimicrobial class (65% of the antibiotic users), followed by cephalosporins (39%) and macrolides (37%).

A total of 86% of anti-asthmatic users received at least one prescription of inhaled steroids, while 54% received adrenergic drugs (alone or in fixed combination with other anti-asthmatics).

A total of 620 drugs were prescribed. Amoxicillin+clavulanic acid was the most common (24% of children), followed by inhaled beclometasone (15%) and amoxicillin (14%). (Table 9)

The 10 most prescribed drugs, 6 of which were antibiotics, represented 64% of the prescribed packages and covered 89% of children receiving at least one drug prescription.

A total of 41 drugs, belonging to 12 main ATC therapeutic groups, comprised 90% of the prescribed packages. In particular: 15 were antibiotics, 8 were anti-asthmatics and 6 were anti-histamines.

Beclometasone was the most prescribed drug in children <1 year old, while amoxicillin+clavulanic acid was the leading drug in children ≥ 1 year. Although the prevalence differed across ages, 6 of the 10 most prescribed drugs were the same in all

ages. It can thus be concluded that a total of 15 drugs would suffice to address the main therapeutic needs of children, independently of age.

Four age groups shared the same most prescribed drugs. Flunisolide, budesonide and salbutamol in fixed combination with other antiasthmatics ranked among the top 10 drugs only in children < 1 year old, cefixime, azithromycin and ceftibuten in those  $\geq 1$  year, while cetirizine and fluticasone were among the most prescribed in children  $\geq 7$  years and  $\geq 12$ , respectively (Table 9).

A total of 38% of treated children received one drug, 24% two, 15% three, and 23% four or more different drugs. The proportion of children receiving four or more drugs was higher in boys compared to girls (25% versus 22%;  $\chi^2 = 748$ ; d.f.=1;  $p < 0.001$ ) and in 1-4 years olds (30%) compared to children <1 year (22%) and  $\geq 5$  years (17%) ( $\chi^2 = 31,508$ ; d.f.=2;  $p < 0.001$ )



**Table 9 – The ten most prescribed drugs to Italian children by age group**

< 1 year			1-6 years			7-11 years			≥ 12 years			0-13 years		
Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	
Beclometasone	20.6	Co-Amoxiclav	28.4	Co-Amoxiclav	17.9	Co-Amoxiclav	13.1	Co-Amoxiclav	23.6					
Amoxicillin	18.6	Beclometasone	18.0	Beclometasone	10.0	Amoxicillin	7.0	Amoxicillin	14.8					
Co-Amoxiclav	18.1	Amoxicillin	17.2	Amoxicillin	9.2	Clarithromycin	7.0	Clarithromycin	14.1					
Salbutamol	14.3	Clarithromycin	13.2	Clarithromycin	9.0	Beclometasone	6.8	Beclometasone	11.4					
Betamethasone	9.3	Salbutamol	12.9	Azithromycin	7.3	Azithromycin	5.6	Azithromycin	10.4					
Clarithromycin	8.8	Azithromycin	10.2	Salbutamol	6.9	Salbutamol	4.5	Salbutamol	8.8					
Salbutamol+others	6.6	Betamethasone	9.4	Cefixime	5.5	Cefixime	4.5	Cefixime	7.7					
Flunisolide	6.3	Cefaclor	9.3	Betamethasone	5.3	Betamethasone	3.8	Betamethasone	6.8					
Cefaclor	5.1	Cefixime	7.3	Cefaclor	4.4	Cetirizine	2.6	Cetirizine	6.5					
Budesonide	4.1	Ceftibuten	6.0	Cetirizine	3.5	Fluticasone	2.0	Fluticasone	4.3					

*b) Distribution of prevalence by local health unit.*

Wide differences were found in prevalence between different LHUs; these ranged between 50.1 and 68.4% ( $p < 0.001$ ). The mean prevalence rate was 59.5% (median 60.3%).

The greatest difference was observed in systemic steroid prevalence, which ranged between 1.1 and 19.9%, with a median of 2%.

Geographical differences were also found. Prescription prevalence was lower in northern Italy (57.3%) and higher in two LHUs in southern Italy (68.3%).

A statistically significant correlation between rank distributions at LHU level of the overall prevalence rate and of the prevalence of the four most prescribed therapeutic classes was found. The rank correlation was close, especially with antibiotics ( $r_s=0.99$ ; d.f.=20;  $p<0.0001$ ) and systemic steroids ( $r_s=0.82$ ; d.f.=20;  $p=0.0002$ ), as well as between antibiotic and systemic steroid prevalence ( $r_s=0.84$ ; d.f.=20;  $p=0.0001$ ). On the contrary, no statistically significant rank correlation was found between anti-asthmatic and systemic steroid prevalence ( $r_s=0.37$ ; d.f.=20;  $p=0.095$ ), while a weak correlation was found between anti-asthmatic and anti-histamine prevalence ( $r_s=0.42$ ; d.f.=20;  $p=0.042$ ).

*c) Trend in the 2000-2006 period.*

Prescription prevalence increased between 2000-2002 from 61.5 to 66.9% and decreased afterwards. The prevalence of antibiotics and anti-asthmatics increased in 2006 by 6 and 19%, respectively, compared to 2000.

A total of eight of the 10 most prescribed drugs for each year were the same in the 2000-2006 period.

Beclometasone was the most prescribed drug in 2000 and 2001, while it was replaced by amoxicillin+clavulanic acid from 2002 onwards. The prescription prevalence trend for the ten most prescribed drugs was quite similar to the overall trend, with the exception of amoxicillin+clavulanic acid, whose prevalence increased steadily from 13.2 to 24.4%. The 2006 prevalence was higher than in 2000 for most of these drugs, with the exception of cefaclor and ceftibuten, whose prevalence decreased, and beclometasone, whose prevalence did not change. Amoxicillin+clavulanic acid and salbutamol were the drugs with the highest percentage increase in prevalence (86 and 73%, respectively).

#### *d) Expenditure*

The total expenditure in 2006 was 37 million Euros (2.4% of overall pharmaceutical expenditure in the ARNO sample). The mean expenditure for each treated child was 66 €, was higher for males than females (70 versus 60 €), and increased with increasing age, reaching the highest value in 13 year old children (85€).

Amoxicillin+clavulanic acid was the drug with the highest expenditure (14.5% of the overall), followed by clarithromycin (11.6%) and azithromycin (7.1%). A total of six drugs (the former, plus beclometasone, cefixime and montelukast) accounted for 50% of the expenditure, while the first 30 drugs in order of expenditure accounted for 90%.

### **C. DIFFERENCES BETWEEN LOCAL HEALTH UNITS**

#### **1. Aim of the study**

The aim of this study was to evaluate the intraregional differences in the drug prescribing to children and adolescents.

## 2. Methods

The analysis involved all paediatric prescriptions reimbursed by the Health Service and dispensed by the retail pharmacies of all the 15 LHUs in the Lombardy Region, between 1 January and 31 December 2005.

The study population was composed of 1,543,203 children and adolescents under 18 years of age, male/female ratio 1.06, living in the Lombardy Region. The study sample represented 15% of the Italian paediatric population.

The number of youths under 18 years of age by LHU varied between 15,790 and 189,238.

Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group.

Moreover, a Mantel-Haentzel  $\chi^2$  test was performed in order to compare the drug prescription prevalence in boys and girls.

The area under the prevalence-time curve (AUC) from time 0 to 18 years (data plotted at mid-time interval) were calculated according to the linear trapezoidal rule.

The relationship between the prevalence of the most prescribed therapeutic classes and between the prevalence in the paediatric and adult population by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

The rate of hospitalisation was used as an indicator of the frequency of severe cases of the diseases. The rate of hospitalisation was estimated considering hospital discharge forms, by dividing the number of patients <18 years old hospitalised at least once during 2005 by the total number of residents <18 years old. Hospitalisations associated with a ICD-9 diagnosis code between V30-V39 (Liveborn infants according to type of birth) were excluded.

The relationship between the prevalence and hospitalisation rates by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

The coefficient of variation (ratio between standard deviation and mean) was estimated for the prevalence of each of the 10 drugs most commonly prescribed in all the 15 LHUs.

A stepwise multivariate logistic regression method was used to assess the effect of the covariates on the chance of receiving  $\geq 1$  drug prescriptions (dependent variable).

The following independent variables were tested: age and gender of the child, LHU of residence; kind of physician who was in charge of the patient (paediatrician, general practitioner) and physician gender.

Age was treated as a categorical variable, dividing it into four classes (<1 year, 1-5 years, 6-12 years, 13-17 years).

k-1 dummy variables were used, selecting one reference for each variable. The interaction between variables were not taken into account.

Statistical analysis was performed using SAS software, version 9.1.

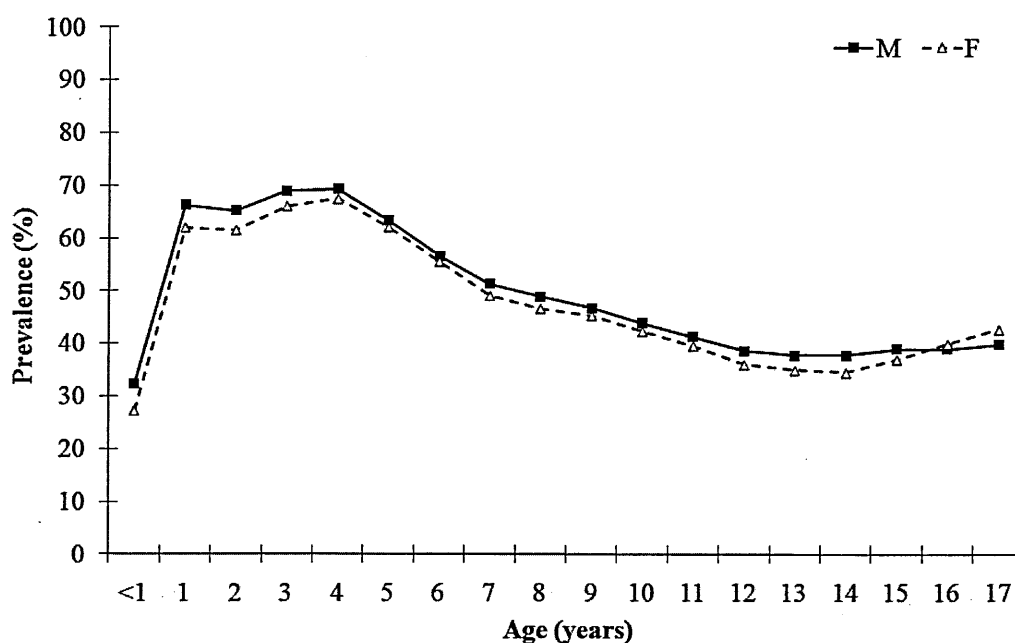
A P value < 0.05 was considered statistically significant.

### **3. Results**

#### *a) Drug prescribing pattern in the Lombardy Region*

In all, 747,790 children and adolescents (48.5% of the population) received at least one drug prescription. The highest prevalence was observed in the 1-5 year old age range (average value 65%), and then decreased to 38% in the 12-17 year range. (Figure 11).

**Figure 11 –Prescription prevalence by gender and age**



The prevalence was slightly higher in boys than girls for all ages ( $\chi^2 = 641$ ; d.f.=1;  $p < 0.001$ ) with the exception of 16 and 17 year old adolescents. The trend for gender was similar up to 14 years of age, after which the prevalence increased in girls.

The AUC<sub>0-18</sub> male/female ratio was 1.04.

In all, 1165 paediatricians prescribed drugs to 65% of the children, while 6791 general practitioners prescribed drugs to 35% of the children. Each paediatrician prescribed drugs to a median of 437 children, while general practitioners prescribed them to a median of 29 children or adolescents.

A total of 2,177,469 prescriptions were dispensed, corresponding to 3,122,745 medication packages. Each treated child received an average of 2.9 prescriptions (median 2) and 4.2 packages (median 2). Boys received a greater average number of prescriptions (2.9 versus 2.7) and packages (4.3 versus 3.9) compared to girls.

The highest number of prescriptions/treated child was observed in children 1-5 years old (3.3; median 3).

In all, 25% of treated children received one package only, while 20% received more than 6 packages. The rate of children receiving six or more packages was higher in males than females (21 versus 19%;  $\chi^2 = 758$ ; d.f.=1;  $p < 0.001$ ), and in children 1-5 years old (25%) compared to those <1 year (9%) and 6-11 years (18%) ( $\chi^2 = 6678$ ; d.f.=2;  $p < 0.001$ ).

Antibiotics were the most prescribed therapeutic class (41% of the population), followed by anti-asthmatics (15%) and anti-histamines (5%). Altogether, these three therapeutic classes comprised 81% of the prescribed packages.

In all, 65% of treated children received drugs belonging to one therapeutic class only, while 28% received drugs belonging to two classes (mainly antibiotics and anti-asthmatics, prescribed to 24% of treated children), and 7% to 3 or more classes (3% received antibiotics, anti-asthmatics, and anti-histamines).

The trend for antibiotics was similar to the overall prevalence trend, while the highest value of anti-asthmatic prevalence was observed at 1 year (29%). The prevalence of anti-asthmatics reached a second age-dependent peak at 4 years (26%).

The prevalence of anti-histamines increased with increasing age, reaching a maximum of 6% at 16 years.

The AUC<sub>0-18</sub> male/female ratio was 1.03 for antibiotics, 1.21 for anti-asthmatics and 1.32 for anti-histamines.

In all, 757 drugs were prescribed. Amoxicillin+clavulanic acid was the most prescribed drug (18% of children), followed by amoxicillin (13%) and inhaled beclometasone (9%) (Table 10). The 10 most prescribed drugs, 7 of which were antibiotics, represented 64% of the prescribed packages.

A total of 70 drugs, belonging to 22 main therapeutic groups of the ATC classification, comprised 90% of the prescribed packages. In particular: 23 were antibiotics, 13 were

anti-asthmatics and 6 were anti-histamines. Seven second and third generation cephalosporins (out of 20 prescribed) were among these 70 drugs.

Amoxicillin was the most prescribed drug in children <1 year old, while amoxicillin+clavulanic acid was the leading drug in children  $\geq 1$  year. Although the prevalence differed across ages, 6 of the 10 most prescribed drugs were the same in all ages.

Salbutamol in fixed combination with other antiasthmatics (beclometasone, flunisolide) ranked among the top 10 drugs only in children < 1 year old and flunisolide in those  $\leq 6$  years old. Azithromycin was among the ten most prescribed drugs in children  $\geq 1$  year, cetirizine in children  $\geq 6$  years, and desloratadine and levocetirizine in adolescents  $\geq 12$  years. (Table 10).



**Table 10 – The ten most prescribed drugs by age group in the Lombardy Region.**

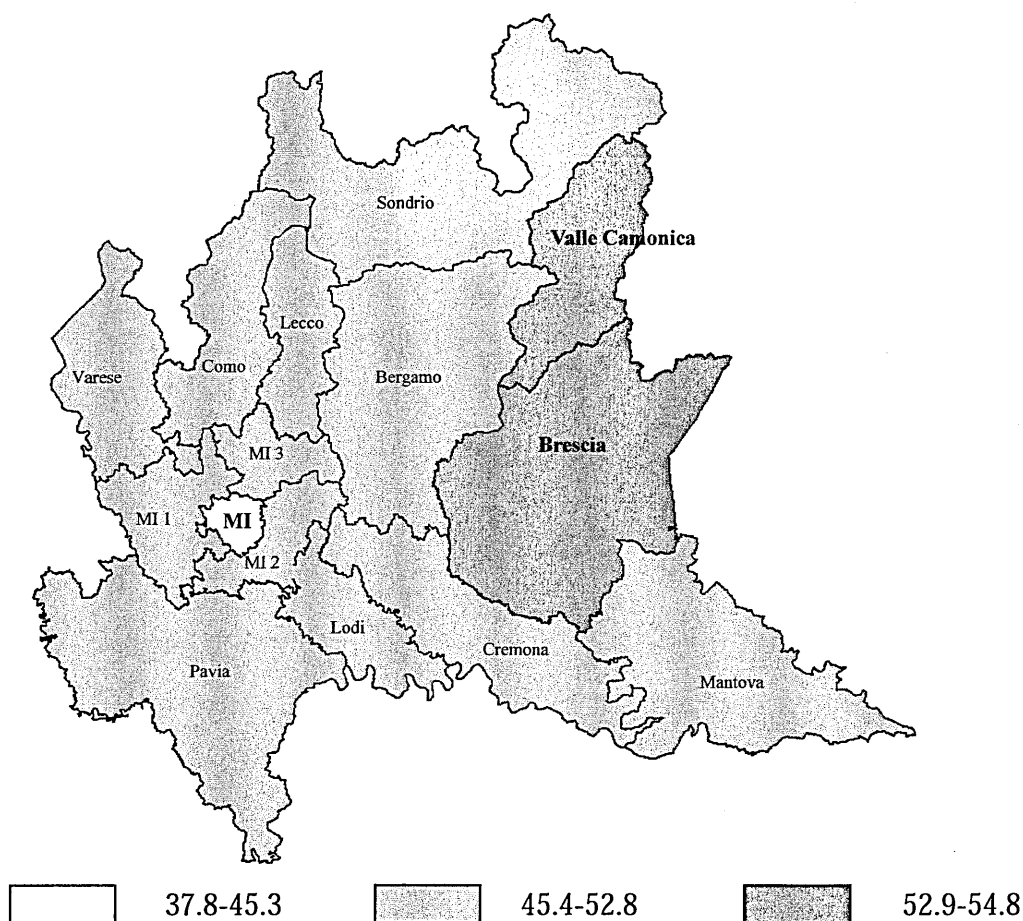
< 1 year			1-5 years			6-11 years			12-17 years			0-17 years		
Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	Drug	%	
Amoxicillin	10.7	Co-Amoxiclav	29.7	Co-Amoxiclav	16.8	Co-Amoxiclav	10.4	Co-Amoxiclav	17.9	Co-Amoxiclav	17.9	Co-Amoxiclav	17.9	
Beclometasone	9.5	Amoxicillin	23.1	Amoxicillin	11.1	Amoxicillin	7.0	Amoxicillin	13.1	Amoxicillin	13.1	Amoxicillin	13.1	
Co-Amoxiclav	7.7	Beclometasone	16.3	Beclometasone	7.8	Clarithromycin	5.1	Clarithromycin	9.1	Beclometasone	9.1	Beclometasone	9.1	
Salbutamol	6.7	Cefaclor	11.5	Clarithromycin	7.2	Azithromycin	4.4	Azithromycin	7.0	Clarithromycin	7.0	Clarithromycin	7.0	
Cefaclor	3.3	Salbutamol	11.2	Salbutamol	5.2	Beclometasone	4.0	Beclometasone	6.1	Salbutamol	6.1	Salbutamol	6.1	
Flunisolide	2.3	Clarithromycin	9.9	Azithromycin	5.3	Cefixime	2.6	Cefixime	5.3	Cefaclor	5.3	Cefaclor	5.3	
Clarithromycin	1.9	Azithromycin	7.0	Cefaclor	4.7	Salbutamol	2.5	Salbutamol	5.2	Azithromycin	5.2	Azithromycin	5.2	
Salbutamol+others	1.1	Cefixime	5.6	Cefixime	3.8	Cetirizine	2.2	Cetirizine	3.8	Cefixime	3.8	Cefixime	3.8	
Ceftibuten	1.0	Ceftibuten	4.5	Cetirizine	2.7	Desloratadine	1.1	Desloratadine	2.3	Ceftibuten	2.3	Ceftibuten	2.3	
Cefixime	1.0	Flunisolide	3.3	Ceftibuten	2.0	Levocetirizine	0.9	Levocetirizine	2.2	Cetirizine	2.2	Cetirizine	2.2	

In all, 253 drugs of the total 757 (33%) were prescribed to children of all the age groups, while 538 drugs (71%) were prescribed in children  $\geq 1$  year.

In all, 49% of treated children received one drug, 25% two, 13% three, and 13% four or more different drugs. The proportion of children receiving four or more drugs was higher in boys compared to girls (14 versus 12%;  $\chi^2 = 748$ ; d.f.=1;  $p < 0.001$ ) and in children 1-5 years old (19%) compared to those  $< 1$  year (9%) and  $\geq 6$  years (9%) ( $\chi^2 = 8376$ ; d.f.=2;  $p < 0.001$ ).

*b) Distribution of prevalence by local health unit.*

**Figure 12 – Distribution of the prescription prevalence by Lombardy Region's local health unit**



Large differences were found in prevalence between different LHUs; these ranged between 38.4 in Milan and 54.8% in Brescia (Figure 12). The mean prevalence was 49.1% (median 49.2%). The distribution of the prescription rate (mean number of prescriptions by treated child) was similar, ranging from 2.65 in Milan to 3.31 in Brescia.

The prevalence of antibiotics ranged between 32.2 in Milan and 49.0% in Brescia, that of anti-asthmatics ranged between 10.1 in Milan and 20.1% in Mantova and that of anti-histamines ranged between 3.3 in Milan and 6.0% in Sondrio.

A statistically significant correlation between rank distributions at LHU level of the overall prescription prevalence and antibiotic ( $r_s = 0.99$ ; d.f.=13;  $p < 0.0001$ ) and anti-asthmatic prevalence ( $r_s = 0.66$ ; d.f.=13;  $p = 0.007$ ) was found. On the contrary, no statistically significant rank correlation was found between overall and anti-histamine prevalence ( $r_s = 0.23$ ; d.f.=13;  $p = 0.40$ ).

In the adult population (18-64 years) the prevalence ranged between 47.8 in Milan and 58.6% in Valle Camonica. A statistically significant correlation between rank distributions at LHU level of the paediatric and adult prescription prevalence was found ( $r_s = 0.80$ ; d.f.=13;  $p = 0.0003$ ).

On the contrary, no correlation was found between rank distribution at LHU level of the prevalence and hospitalisation rates in the paediatric population ( $r_s = 0.32$ ; d.f.=13;  $p = 0.24$ ). The hospitalisation rate ranged between 7.1% in Mantova and 9.8% in Milan-1 (one of the three LHUs of the province of Milan). In this regard, the rates in Milan and Brescia were similar (8.7 and 8.9%, respectively), despite the fact that they ranked as opposites in prescription prevalence.

The total number of drugs prescribed to the paediatric population in each LHU ranged between 294 and 593. Only 204 drugs were prescribed in all the 15 LHUs, and 8 were among the 10 leading drugs in all the LHUs (amoxi-clavulanic, amoxicillin,

beclometasone, clarithromycin, azithromycin, salbutamol, cefixime, cefaclor). Among them, cefixime was the one with the greatest coefficient of variation (0.36), followed by cefaclor and azithromycin (0.29). Amoxi-clavulanic acid, the drug with the lowest CV (0.15), was the most prescribed drug in 13 LHU, while amoxicillin was the leading drug in the other two (Valle Camonica and Milan-3).

A total of 14 drugs were among the top 10 in all the 15 LHUs.

*c) Multivariate analysis*

Table 11 summarises the results of the multivariate analysis. The age and residence of the child were the main determinants of drug exposure. In particular, being 1-5 years old (OR 4.51; 95%CI 4.43 - 4.58) and living in Brescia (OR 2.08; 95% CI 2.06 - 2.11) were the factors associated with the highest risk of drug exposure.

Male gender and having a female general practitioner also slightly increased the probability of receiving a drug prescription.

**Table 11 – Results of the multivariate analysis.**

		Unadjusted OR	Adjusted OR
Variables		(95% CI)	(95% CI)
Age group (years)	<1	reference	reference
	1-5	4.40 (4.32 - 4.47)	4.51 (4.43 - 4.58)
	6-11	2.11 (2.07 - 2.14)	2.11 (2.08 - 2.14)
	12-17	1.43 (1.41 - 1.46)	1.41 (1.39 - 1.43)
Gender	F	reference	reference
	M	1.08 (1.07 - 1.09)	1.09 (1.08 - 1.10)

LHU	Milano	reference	reference
	Brescia	1.92 (1.89 – 1.94)	2.08 (2.06 - 2.11)
	Valle Camonica	1.82 (1.76 – 1.89)	2.06 (1.99 - 2.13)
	Mantova	1.72 (1.68 - 1.75)	1.88 (1.85 - 1.92)
	Cremona	1.63 (1.60 - 1.66)	1.76 (1.72 - 1.80)
	Lodi	1.64 (1.60 - 1.68)	1.80 (1.76 - 1.85 )
	Milano-1	1.61 (1.58 - 1.63)	1.71 (1.68 - 1.73)
	Pavia	1.56 (1.53 - 1.58)	1.66 (1.63 - 1.69)
	Como	1.54 (1.51 - 1.56)	1.67 (1.64 - 1.70)
	Bergamo	1.51 (1.49 - 1.53)	1.63 (1.61 - 1.65)
	Milano-3	1.48 (1.46 - 1.50)	1.57 (1.55 - 1.59)
	Varese	1.45 (1.43 - 1.47)	1.57 (1.54 - 1.59)
	Lecco	1.45 (1.43 - 1.48)	1.55 (1.52 - 1.58)
	Sondrio	1.41 (1.38 - 1.45)	1.53 (1.49 - 1.57)
	Milano-2	1.39 (1.37 - 1.42)	1.48 (1.46 - 1.51)
Prescriber	Paediatrician	reference	reference
	General		
	Practitioner	0.65 (0.65- 0.66)	1.06 (1.05 - 1.07)
Prescriber gender	F	reference	reference
	M	0.84 (0.83 - 0.84)	0.92 (0.91 - 0.93)

## D. DIFFERENCES BETWEEN DISTRICTS

### 1. Aim of the study

The aim of this study was to evaluate the differences in the drug prescribing to children and adolescents between the healthcare districts of a local health unit.

## 2. Methods

The analysis involved all paediatric prescriptions reimbursed by the Health Service and dispensed by the retail pharmacies of Milan local health unit in the Lombardy Region, between 1 January and 31 December 2005. Milan was chosen since it was the one with the lowest prevalence of drug prescription among the LHUs in Lombardy region.

The study population was composed of 122,714 children and adolescents under 18 years of age, male/female ratio 1.06. The study sample represented 12% of the Lombardy Region paediatric population. The population per district ranged between 20,145 and 47,316 youths

Prevalence data by sex and age were calculated by dividing the number of drug users by the total number of male and female residents in each age group.

Moreover, a Mantel-Haentzel  $\chi^2$  test was performed in order to compare the drug prescription prevalence in boys and girls.

The area under the prevalence-time curve (AUC) from time 0 to 18 years (data plotted at mid-time interval) were calculated according to the linear trapezoidal rule.

The relationship between the prevalence of the most prescribed therapeutic classes and between the prescription prevalence in the paediatric and adult population by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

The rate of hospitalisation was used as an indicator of the frequency of severe cases of the diseases. The rate of hospitalisation was estimated considering hospital discharge forms, by dividing the number of patients <18 years old hospitalised at least once during 2005 by the total number of residents <18 years old. Hospitalisations associated with a ICD-9 diagnosis code between V30-V39 (Liveborn infants according to type of birth) were excluded.

The relationship between the prevalence and hospitalisation rates by local health unit was investigated using the non-parametric Spearman Rank Correlation test.

The coefficient of variation (CV; ratio between the standard deviation and the mean) was estimated for the prevalence of each of the 10 drugs most commonly prescribed in all the 5 districts.

### **3. Results**

#### *a) Drug prescribing pattern in the Milan LHU*

During 2005, 70,888 children and adolescents (38.8% of the population) received at least one drug prescription. The highest prevalence was observed in the 1-5 year old age range (average value 54%), and then decreased to 29% in the 12-17 year range.

The prevalence was slightly higher in boys than girls for all ages ( $\chi^2 = 58.5$ ; d.f.=1;  $p < 0.001$ ) with the exception of 16 and 17 year old adolescents. The trend for gender was similar up to 14 years of age, after which the prevalence increased in girls.

The AUC0-18 male/female ratio was 1.04.

In all, 134 paediatricians prescribed drugs to 71% of the children, while 1006 general practitioners prescribed drugs to 29% of the children. Each paediatrician prescribed drugs to a median of 376 children, while general practitioners prescribed them to a median of 18 children or adolescents.

A total of 187,808 prescriptions were dispensed, corresponding to 284,472 medication packages. Each treated child received an average of 2.7 prescriptions (median 2) and 4.0 packages (median 2). Boys received a greater average number of prescriptions (2.8 versus 2.5) and packages (4.2 versus 3.8) compared to girls.

The highest number of prescriptions/treated child was observed in children 1-5 years old (2.9; median 2).

In all, 24% of treated children received one package only, while 18% received more than 6 packages. The rate of children receiving six or more packages was higher in males than females (20 versus 17%;  $\chi^2 = 118$ ; d.f.=1;  $p < 0.001$ ), and in children 1-5 years old (21%) compared to those <1 year (8%) and 6-17 years (16%) ( $\chi^2 = 378$ ; d.f.=2;  $p < 0.001$ ).

Antibiotics were the most prescribed therapeutic class (33% of the population), followed by anti-asthmatics (11%) and anti-histamines (3%). Altogether, these three therapeutic classes comprised 80% of the prescribed packages.

The trend for antibiotics was similar to the overall prevalence trend, while the highest value of anti-asthmatic prevalence was observed at 1 year (25%).

The prevalence of anti-histamines increased with increasing age, reaching a maximum of 5% at 17 years.

The AUC<sub>0-18</sub> male/female ratio was 1.03 for antibiotics, 1.21 for anti-asthmatics and 1.32 for anti-histamines.

In all, 511 drugs were prescribed. Amoxicillin+clavulanic acid was the most prescribed drug (15% of children), followed by amoxicillin (12%) and inhaled beclometasone (7%) (Table 12).

The 10 most prescribed drugs, 6 of which were antibiotics, represented 66% of the prescribed packages.

Amoxicillin was the most prescribed drug in children <1 year old, while amoxicillin+clavulanic acid was the leading drug in children  $\geq 1$  year. Although the prevalence differed across ages, 6 of the 10 most prescribed drugs were the same in all ages.

Aciclovir ranked among the top 10 drugs only in children < 1 year old and flunisolide in those  $\leq 6$  years old. Azithromycin was among the ten most prescribed drugs in children



$\geq 1$  year, cetirizine in children  $\geq 6$  years, and desloratadine and levocetirizine in adolescents  $\geq 12$  years. (Table 12).

Table 12 – The ten most prescribed drugs by age group in Milan LHM

Drug	< 1 year		1-5 years		6-11 years		12-17 years		0-17 years	
	Drug	%	Drug	%	Drug	%	Drug	%	Drug	%
Amoxicillin	Amoxicillin	10.0	Co-Amoxiclav	26.1	Co-Amoxiclav	14.0	Co-Amoxiclav	7.6	Co-Amoxiclav	15.3
Beclometasone	Beclometasone	7.2	Amoxicillin	22.9	Amoxicillin	9.0	Amoxicillin	4.8	Amoxicillin	12.0
Co-Amoxiclav	Co-Amoxiclav	6.6	Beclometasone	12.2	Clarithromycin	5.5	Clarithromycin	3.8	Beclometasone	6.5
Salbutamol	Salbutamol	5.7	Salbutamol	9.0	Beclometasone	5.0	Azithromycin	3.1	Clarithromycin	5.3
Clarithromycin	Clarithromycin	5.7	Clarithromycin	7.4	Salbutamol	3.8	Beclometasone	2.4	Salbutamol	4.5
Flunisolide	Flunisolide	1.5	Cefaclor	5.3	Azithromycin	3.0	Cetirizine	2.1	Azithromycin	3.1
Cefaclor	Cefaclor	1.4	Azithromycin	3.7	Cefaclor	2.5	Salbutamol	2.1	Cefaclor	2.6
Acyclovir	Acyclovir	1.0	Cefixime	3.0	Cetirizine	2.1	Cefixime	1.4	Cefixime	1.9
Ceftibuten	Ceftibuten	0.6	Flunisolide	2.1	Cefixime	1.8	Levocetirizine	0.8	Cetirizine	1.6
Cefixime	Cefixime	0.6	Ceftibuten	2.0	Fluticasone	1.0	Desloratadine	0.8	Flunisolide	1.1

*b) Distribution of prevalence by district.*

Differences were found in prescription prevalence between different districts; these ranged between 33.4 and 40.4% , while no differences were found in the mean number of prescriptions by treated child. (Table 13)

**Table 13 – Distribution of the prevalence of drug prescription and hospitalisation by district**

District	Paediatric Prevalence (%)	Prescriptions per treated children	Adult Prevalence (%)	Paediatric Hospitalisation (%)
1	33.4	2.6	44.1	8.7
2	40.4	2.7	51.1	9.4
3	38.2	2.7	47.5	8.5
4	40.0	2.6	49.9	9.0
5	40.2	2.7	49.9	8.3

The prevalence of antibiotics ranged between 28.8 and 34.0, that of anti-asthmatics ranged between 8.6 and 11.7% , and that of anti-histamines ranged between 1.9 and 4.0% .

In all the cases the lowest prevalence was observed in the district number 1 (corresponding to the centre of Milan).

In the adult population (18-64 years) the prevalence ranged between 44.1 and 51.1%. A strong correlation between rank distributions at district level of the paediatric and adult prescription prevalence was found, although not statistically significant ( $r_s=0.98$ ; d.f.=3;  $p=0.05$ ).

### Table 14 – The ten most prescribed drugs by Milan LHU district

1	2	3	4	5
Drug	%	Drug	%	Drug
Co-Amoxiclav	14.9	Co-Amoxiclav	15.4	Co-Amoxiclav
Amoxicillin	9.8	Amoxicillin	10.9	Amoxicillin
Clarithromycin	5.1	Beclometasone	7.1	Beclometasone
Beclometasone	4.6	Salbutamol	5.6	Clarithromycin
Salbutamol	3.3	Clarithromycin	5.0	Salbutamol
Cefaclor	2.5	Cefaclor	2.9	Azithromycin
Azithromycin	2.4	Azithromycin	2.9	Azithromycin
Cefixime	1.6	Cetirizine	1.9	Cefaclor
Salbut+ipratrop	1.5	Cefixime	1.6	Cetirizine
Flunisolide	1.0	Ceftibuten	1.2	Cetirizine
			1.4	Cefpodoxime
			1.7	Fluticasone

On the contrary, no correlation was found between rank distribution at district level of the prevalence and hospitalisation rates in the paediatric population ( $r_s=0.30$ ; d.f.=3;  $p=0.55$ ). The hospitalisation rate ranged between 8.3% and 9.4%.

The total number of drugs prescribed to the paediatric population in each district ranged between 264 and 370. Only 201 drugs were prescribed in all the 5 districts, and 8 were among the 10 leading drugs in all of them (amoxi-clavulanic, amoxicillin, beclometasone, clarithromycin, azithromycin, salbutamol, cefixime, cefaclor). (Table 14) Among them, cefixime and salbutamol were those with the greatest coefficient of variation (0.18), while amoxi-clavulanic acid was the drug with the lowest ratio (0.03). A total of 14 drugs were among the top 10 in all the 5 districts.

In all, 22 drugs were prescribed by more than 75% of paediatricians and 10 drugs were prescribed by all the paediatricians.

### *c) Multivariate analysis*

Table 15 summarises the results of the multivariate analysis. The age and residence of the child were the main determinants of drug exposure. In particular, being 1-5 years old (OR 3.83; 95%CI 3.65 - 4.02) and living outside the centre of Milan (OR 1.43; 95% CI 1.39 – 1.48) were the factors associated with the highest risk of drug exposure.

Male gender and having a female general practitioner also slightly increased the probability of receiving a drug prescription.

**Table 15 – Results of the multivariate analysis (determinants of drug prescription in the Milan LHU).**

Variables		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age group (years)	<1	reference	reference
	1-5	3.79 (3.61- 3.97)	3.83 (3.65- 4.02)
	6-11	1.83 (1.74 – 1.92)	1.82 (1.73 – 1.91)
	12-17	1.33 (1.27 - 1.40)	1.29 (1.23 - 1.36)
Gender	F	reference	reference
	M	1.08 (1.05 - 1.10)	1.08 (1.06 - 1.10)
District	1	reference	reference
	5	1.34 (1.29 – 1.39)	1.53 (1.47 – 1.59)
	2	1.35 (1.30 – 1.40)	1.46 (1.41 – 1.52)
	4	1.32 (1.28 - 1.37)	1.46 (1.41 - 1.52)
	3	1.23 (1.19 - 1.28)	1.30 (1.25 - 1.35)
Prescriber	Paediatrician	reference	reference
	General		
	Practitioner	0.67 (0.65-0.68)	1.04 (1.01 - 1.07)
Prescriber gender	F	reference	reference
	M	0.80 (0.79 - 0.82)	0.95 (0.93 - 0.97)

## **E. DISCUSSION**

### **1. Strengths and limitations**

The studies presented above monitored the drug prescribing to children and adolescents in large populations, at different level (national, regional, local), and took into consideration several potential determinants of drug prescriptions.

However, these studies have also some limitations. The first, common to many studies based on prescription databases, is the lack of information concerning the diseases for which drugs are prescribed.

The second is the lack of data concerning drugs without state reimbursement and over the counter drugs. It was therefore not possible to evaluate the prescription pattern of some drugs commonly prescribed to children, e.g. paracetamol and antitussive medications.

On the other hand, most antibiotics and nearly all chronic disease therapies are reimbursed by the national health service, and it was therefore possible to monitor nearly all the drugs relevant for disease treatment in childhood.

Despite the above limitations, the findings are therefore representative of prescribing patterns in the Italian outpatient population.

### **2. Prescribing pattern**

The profile observed in these studies is quite similar, in terms of rate, gender, and age differences and therapeutic classes most frequently prescribed, to those previously observed in national and international settings.<sup>25-29,37,44</sup>

Some findings seem to be specific to Italy, however.

First of all, Italian children are exposed to a high number of drugs. Nearly ¼ of the children treated received four or more drugs and 1/10 more than 9 packages (corresponding to a prevalence of 7% in the paediatric population).

Pre-schoolers are the most exposed to drugs, especially 3-4 years old, a finding consistent with the increased incidence of infections upon entry into the community.

However, the finding that 1/3 of children aged 1 to 4 years old needing a drug therapy received more than five packages/year and more than four different medications is of concern.

The huge number of drugs prescribed is another finding that seems peculiar to the Italian situation. Despite this plethora of medications, 15 drugs seem to be sufficient to cover the most common diseases independently of age and geographical setting.

Antibiotics were the most prescribed type of drugs: they were prescribed to 9 of 10 children receiving a prescription. The prevalence reported in the Italian paediatric population is 3 fold higher than that in the Netherlands or United Kingdom.<sup>97</sup>

Despite this fact, a 6% increase in the antibiotic annual prevalence was observed in the 2000-2006 period.

Amoxicillin+clavulanic acid was the most prescribed drug almost in all the setting evaluated (at the national, regional and local level) and its prevalence nearly doubled in the 2000-2006 period; on the contrary, several international guidelines consider amoxicillin alone the first choice of treatment for the most common childhood infections (acute otitis media, pharyngo-tonsillitis, sinusitis).<sup>90-93</sup> Despite in other countries amoxicillin is the most prescribed antibiotic,<sup>97</sup> it could be hypothesised that in Italy amoxicillin+clavulanic acid was probably preferred due to its twice daily schedule regimen that it is supposed to get a better compliance compared to the amoxicillin dosage schedule, to an unproved concern of beta-lactamase producing bacteria, and to the market availability (since 2002) of a more tolerable suspension with an amoxicillin-clavulanic acid 7:1 ratio, instead of 4:1

Moreover, independently from the setting, nearly 40% of children receiving antibiotics were prescribed cephalosporins or macrolides, second line agents likely chosen, more



often than not, not on the basis of safety and efficacy data, but because of palatability and shorter length of therapies.

The profile of anti-asthmatic drug prescriptions was similar to that previously described (frequent use of inhaled steroids, in particular nebulised beclometasone, occasionally prescribed to pre-school children) and suggests that the prescriptions concerning these drugs are often inappropriate.<sup>57,58</sup>

The prevalence of anti-asthmatic drug prescriptions was higher than both the prevalence of asthma in Italy and the estimated rate in other paediatric contexts. Furthermore, 60% of the children treated with anti-asthmatics are under 6 years old, while most episodes of wheezing that appear in pre-school children disappear with age and it is difficult to diagnose asthma in children under 6 years old.<sup>98,99</sup>

Moreover, the lack of correlation between the anti-asthmatic and anti-histamine or systemic steroid prevalence is indicative of the fact that anti-asthmatic drugs are often prescribed for diseases different from asthma, as observed in other studies that reported a wide use of nebulised steroids in Italy as prophylaxis or treatment for viral wheezing.<sup>29</sup> On the contrary, a correlation between high use of anti-asthmatics ( $\geq 4$  packages/year) and anti-histamine or systemic steroid prevalence was found, as reported in chapter VIII. The fact that in Italy nebulised beclometasone is also licensed for rhinopharyngitis, and the misbelief that it could relieve inflammation due to infections could have contributed to its high prescription prevalence.<sup>100</sup>

The prescribing pattern of systemic steroids also appears inappropriate, since 65% of treated youths received only one box and the highest prevalence was observed in 1 year old children. The most prescribed drug was betamethasone (96% of systemic steroid users), available in Italy as dispersible tablets and often prescribed for treatment of upper respiratory tract infections.<sup>29</sup> Steroid prevalence varied widely between local health units, with a 19:1 ratio between the highest and lowest values. Even if systemic

steroids in infancy may be appropriately used as treatment of croup, the strong correlation between antibiotic and systemic steroid prevalence, and its geographical clustering seem to support the hypothesis that betamethasone is commonly used for the treatment of respiratory infections and the fact that inappropriate drug use is more frequent in a few contexts.

The youngest children, in particular infants, are more likely to receive drugs with a questionable evidence base. The population of children < 1 year old was, in fact, characterised by a wide use of steroids, either as an inhaled formulation or as systemic use.

In Italy beclometasone was the most prescribed drug in children <1 year old (prevalence 21%). Flunisolide and budesonide can be considered quite “typical” of this population, since they ranked among the 10 most prescribed drugs only in children <1 year old, with a prevalence of 6% and 4% respectively. Moreover, 9% of infants were prescribed betamethasone.

Prescription prevalence did not change in the 2000-2006 period. Periodic reports have been released since 2000, with the aim to share prescription data with healthcare professionals at the national and local level and to implement the rational use of drugs in the paediatric population.<sup>94,101</sup> Furthermore, several Italian drug utilisation studies were published in the 2000-2006 period (in particular concerning antibiotics and anti-asthmatics),<sup>29,44-46,57,58</sup> but they had little impact on the prescribing habits of practitioners, at least according to these findings.

The case of beclometasone is emblematic: an open letter was published in 2001 to warn paediatricians about the overuse of this drug,<sup>102</sup> despite this initiative, its prevalence did not change even after five years.

Moreover, in 2003 the Italian Ministry of Health published a paediatric formulary entitled “*Guida all’uso dei farmaci per i bambini*” [guide to the use of drugs for

children], a translation and adaptation to the Italian context of “Medicines for Children” and sent it to healthcare professionals. Only 42% of the drugs prescribed to Italian children were quoted in the formulary. Although “Medicines for Children” may reflect attitudes different from those of Italian practitioners, this figure indicates that many drugs have a questionable evidence base.

The expenditure for drugs prescribed to children is negligible when compared with the overall pharmaceutical expenditure (2.4%). Since the need to reduce expenditure is one of the main determinants of programmes to implement the rational use of drugs, a very low expenditure could paradoxically represent a reason to not address the problem. However, the findings from this study indicate that a significant reduction of expenditure could be achieved by simply choosing the less expensive drug among a plethora of me-too medications.

### **3. Differences between settings**

Large inter-regional and intra-regional differences were found in prevalence of drug prescription.

Differences were found also in context characterised by a low drug consumption.

In this regard, the cases of Lombardy Region and Milan are emblematic.

According to data collected by the National Drug Utilization Monitoring Centre (OSMED) of the Italian Drug Agency (AIFA) Lombardy is among the Italian regions with the lowest drug consumption: 776.8 DDD/1000 inhabitants versus a mean of 880.5 (and a maximum of 1019.3).<sup>96</sup> However, a child living in Brescia or Valle Camonica (nearby LHU) has a 2-fold higher risk of receiving a drug prescription than a child living in Milan, independently of her/his age and gender.

Moreover, a child living in suburbs of Milan has a 1.4 higher risk of receiving a drug prescription than a child living in the city centre.

The rank distribution of prevalence in children and adolescents correlates with that in adults; in contrast no correlation was found in hospitalisation rate which could be considered a proxy of disease prevalence (at least of severe cases).

It could therefore be hypothesised that the quantitative and qualitative differences between LHU are not due to a different epidemiology of the diseases, but to other factors like socio-cultural and economic determinants and different prescribing habits between physicians.

Despite these analyses did not consider socio-economic variable, it is likely that in a quite homogeneous setting from a socio-economic point of view like Lombardy region different prescribing habit between physicians is one of the main factor explaining the existing differences. However, the district of the centre of Milan may represent an exception, since the gross income per year of the families living in this area is higher than in other healthcare districts of the Lombardy region. Is therefore possible that families living in the centre of Milan more commonly attend private paediatricians and buy drugs out-of-pocket, and that the prevalence of drug prescription in this district may be underestimated.

However, despite the differences in drug prescription prevalence, the general prescribing profile observed in the Lombardy Region and in Milan is similar to that observed in Italy, with a large use of antibiotics, in particular cephalosporins and macrolides, and inhaled steroids.

In this regard, it is interesting to note that Valle Camonica it is one of the two LHU in which amoxicillin was the most prescribed antibiotic, despite the fact that it is also one of the LHU with the highest prevalence. Thus, a high prevalence is not synonymous with inappropriateness in all cases, and vice versa. In Milan, despite the lowest prevalence, amoxi-clavulanic acid was the most prescribed antibiotic. Moreover, the

prevalence of nebulised beclometasone was not different from the prevalence reported in Valle Camonica.

Moreover, also in a quite homogeneous setting, as a region or a city, a plethora of drugs was prescribed. In all, 757 drugs were prescribed in the Lombardy Region even if less than 30% were prescribed in all the LHUs. The same pattern was observed in Milan, with 201 out of 511 drugs prescribed in all the five districts.

Moreover, only 253 drugs were prescribed to children of all age groups. If infants are excluded from the analysis, however, this number increases to 538. On the contrary, an analysis of the licences of medications marketed in Italy found that a paediatric indication was reported for only 80 drugs, while for 124 a paediatric dosage schedule was reported. This means that for most of the drug prescribed to Italian children and adolescents the information concerning the paediatric use was scant or lacking.

## **F. MAIN CONCLUSIONS**

- The prevalence of drug prescription varied widely among different geographical setting. The province of residence resulted as one of the main determinants of drug prescription.
- More than 600 different drugs were prescribed to children and adolescents, even if 15 drugs seem to be sufficient to cover the most common diseases independently of age and geographical setting.
- A wide use of antibiotic was observed, in particular of second line therapeutic agents, such as cephalosporins.
- Moreover, anti-asthmatic drugs were widely prescribed, in particular nebulised steroids (in particolare beclometasone and flunisolide)

- Educational interventions for health care professionals and parents could be effective in improving the rational drug use. However, more efforts are needed also in certain contexts characterised by a low prescription prevalence, but also by a not always appropriate drug use.

## **VIII. A FOCUS ON TWO DRUG CLASSES**

## **A. USE OF PSYCHOTROPIC MEDICATIONS IN ITALIAN CHILDREN AND ADOLESCENTS.**

### **1. Introduction**

The safety and effectiveness of psychotropic drug use in the paediatric population is widely debated, because of the lack of data concerning the long term effects. Moreover, an increase of suicidal ideation associated with antidepressant use in the paediatric age was reported.<sup>82</sup>

In such a context, a study with the aim to estimate the prevalence of psychotropic drug prescription in the Italian paediatric population and to describe diagnostic and therapeutic approaches was performed.

### **2. Methods**

Pediatric prescriptions of psychotropic drugs reimbursed by the Health Service and dispensed by the retail pharmacies of 27 local health units (which were part of the ARNO project) between 1 January 2004 and 31 December 2004 were analyzed.

The population selected for this study was composed of 1,484,770 children and adolescents less than 18 years of age living in the areas covered by the local health units, representing 14% of the Italian population.

Moreover, the prescription trend in the period 1998-2004 was analyzed in a subset of 16 LHUs for which the data were available for all the years, and the annual prevalence and incidence were calculated. Prevalence was defined as the number of individuals who received at least one psychotropic drug prescription per 1000 individuals in the population and incidence was defined as the number of people who received a psychotropic prescription drug for the first time per 1000 youths in the population.



The prevalence was stratified by drug subgroup, age group (0-5, preschool children; 6-13, school-age children; 14-17, adolescents) and gender.

Psychotropic drugs were defined according to the World Health Organization categories and comprised the following subgroups of the Anatomic Therapeutic Chemical (ATC) classification system: stimulants (ATC group N06BA), antidepressants (N06A), antipsychotics (N05A excluding lithium), lithium (N05AN01). Antidepressants were categorized into 3 subclasses: tricyclic antidepressants (TCAs, N06AA), selective serotonin reuptake inhibitors (SSRIs, N06AB), and “other” antidepressants (N06AX). Anticonvulsants were excluded since in children they are mainly used to treat epilepsy, while anxiolytics were excluded because they are not reimbursed by the Italian National Health Service and were thus not present in the ARNO database.

Significance of the linear trend ( $\chi^2$  trend) was assessed across age groups or years.

Moreover, a Mantel-Haentzel  $\chi^2$  test was performed in order to compare the prevalence of psychotropics in boys and in girls.

In order to evaluate the extent of chronic therapy, among the patients treated with psychotropic drugs in 2004, a sample of youths receiving at least one drug prescription in the previous 3 years was selected. A  $\chi^2$  test was performed in order to compare the rate of chronic treatment in boys versus girls and in antidepressant versus antipsychotic users. Statistical analysis was performed using SPSS 10.1 software and IBM DB2 Intelligent Miner for Data version 6. A P value < 0.05 was considered statistically significant.

### **3. Results**

During 2004, 4316 youths younger than 18 years received psychotropic drugs (2.91/1000 youths). Wide differences were found in the prevalence of psychotropic drug

prescriptions between the different local health units, these ranged between 0.8‰ and 6‰.

Antidepressants were prescribed to 3503 youths (2.36 ‰), antipsychotics to 1005 (0.68‰) and lithium to 73 (0.05‰). The prevalence of psychotropic drug prescriptions increased with increasing age, with a statistically significant trend ( $\chi^2_t = 2443$ ; d.f.=2;  $p < 0.0001$ ), while there was no statistically significant difference in prescription prevalence between males and females. Antidepressants were prescribed mainly to girls ( $\chi^2_{M-H} = 30$ ; d.f.=1;  $p < 0.0001$ ), while the prescription prevalence of antipsychotics was higher in boys ( $\chi^2_{M-H} = 105$ ; d.f.=1;  $p < 0.0001$ ) (table 16).

Co-prescription was rare: 4051 children and adolescents (94% of the treated youths) received only one class of psychotropic medication, 259 children and adolescents (6%) received drugs from two classes (mainly antidepressants and antipsychotics) and only 6 youths received antidepressants, antipsychotics and lithium.

Among youths receiving antidepressant prescriptions, SSRIs were given to 2594 youths (74%), tricyclic antidepressants to 557 (16%), and other antidepressants (mainly trazodone or venlafaxine) to 553 (16%). A total of 190 children and adolescents received antidepressants belonging to two different classes: 89 received drugs in the SSRI and atypical antidepressant classes, and 78 in the SSRI and tricyclic classes.

Table 16 – Psychotropic drug prescription prevalence by gender and age group

Age group (y)	Gender	Antidepressants	Antipsychotics	Lithium	Any psychotropics
0-5	M	0.87	0.17	0.01	1.02
	F	0.85	0.13	0.02	0.96
	M/F (95% C.I.)*	1.03 (0.85-1.24)	0.64 (0.40-1.02)	0.38 (0.07-1.94)	1.06 (0.89-1.27)
6-13	M	1.90	0.88	0.03	2.66
	F	1.58	0.39	0.05	1.95
	M/F (95% C.I.)	1.20 (1.07-1.35) <sup>†</sup>	2.29 (1.86-2.83) <sup>†</sup>	0.69 (0.32-1.51)	1.37 (1.23-1.51) <sup>†</sup>
14-17	M	4.54	1.97	0.14	5.96
	F	7.17	1.07	0.10	7.96
	M/F (95% C.I.)	0.63 (0.58-0.69) <sup>†</sup>	1.85 (1.54-2.22) <sup>†</sup>	1.42 (0.75-2.66)	0.75 (0.69-0.81) <sup>†</sup>
0-17	M	2.15	0.89	0.05	2.85
	F	2.58	0.45	0.05	2.96
	M/F (95% C.I.)	0.83 (0.78-0.89) <sup>†</sup>	1.98 (1.73-2.26) <sup>†</sup>	0.97 (0.60-1.57)	0.96 (0.91-1.02)

\* male/female (M/F) ratio ; <sup>†</sup> p=0.002; <sup>‡</sup> p<0.00001

Table 17 - The 10 most prescribed psychotropic drugs (in order of prevalence) by age group\*.

0-5			6-11			12-17			0-17		
Drug		%	Drug		%	Drug		%	Drug		%
<b>Paroxetine</b>		0.18	<b>Sertraline</b>		0.40	<b>Paroxetine</b>		1.36	<b>Sertraline</b>		0.52
<b>Citalopram</b>		0.16	<b>Paroxetine</b>		0.28	<b>Sertraline</b>		1.33	<b>Paroxetine</b>		0.49
<b>Sertraline</b>		0.13	Risperidone		0.28	<b>Citalopram</b>		1.03	<b>Citalopram</b>		0.38
<b>Venlafaxine</b>		0.09	<b>Citalopram</b>		0.22	<b>Fluoxetine</b>		0.63	Risperidone		0.25
Trazodone		0.08	Trazodone		0.21	<b>Amitriptyline</b>		0.56	<b>Fluoxetine</b>		0.23
<b>Fluoxetine</b>		0.06	<b>Fluoxetine</b>		0.16	Risperidone		0.53	<b>Amitriptyline</b>		0.18
Escitalopram		0.06	<b>Venlafaxine</b>		0.11	Escitalopram		0.51	Trazodone		0.17
Haloperidol		0.04	Imipramine		0.10	Olanzapine		0.31	Escitalopram		0.16
Clomipramine		0.04	Fluvoxamine		0.10	<b>Venlafaxine</b>		0.31	<b>Venlafaxine</b>		0.14
<b>Amitriptyline</b>		0.04	<b>Amitriptyline</b>		0.10	Fluvoxamine		0.27	Fluvoxamine		0.12

\* The most frequently prescribed drugs common to all age groups are reported in bold

A total of 16 antidepressants and 20 antipsychotics were prescribed; sertraline (0.52‰), paroxetine (0.49‰) and citalopram (0.38‰) were the most prescribed antidepressants, risperidone (0.23‰), olanzapine (0.11‰) and haloperidol (0.10‰) the most prescribed antipsychotics.

A total of 14 psychotropic drugs (11 antidepressants and 3 antipsychotics), corresponding to 70% of prescriptions, were among the most prescribed, independently of age (Table 17). Six of these were among the first ten in all the age groups; the first 3 were sertraline, paroxetine and citalopram, respectively. Haloperidol and clomipramine ranked among the ten leading drugs only in pre-school children, imipramine in school age children and olanzapine in the adolescents; risperidone and fluvoxamine were mainly prescribed in children  $\geq 6$  years. Paroxetine was the most prescribed drug in preschoolers and adolescents, and sertraline was the leading drug in children 6-13 years old.

The prevalence of psychotropic prescriptions increased in the period 1998-2004 (Table 18) with a statistically significant trend ( $\chi^2 = 298$ ; d.f.=6;  $p < 0.0001$ ), reaching the highest value in 2002 (3.08‰). The incidence varied with a similar trend ( $\chi^2 = 40$ ; d.f.=6;  $p < 0.0001$ ), with a maximum during 2001 (2.57‰).

The trend of antidepressant prescription prevalence was similar to the overall trend ( $\chi^2 = 501$ ; d.f.=6;  $p < 0.0001$ ); on the contrary, the prevalence of antipsychotics did not increase (Table 18). A 4.5 fold rise in the prescription of SSRIs was observed between 2000 and 2002, while in the same period the prevalence of tricyclics decreased slightly (Figure 13).

The overall prevalence of antidepressant prescriptions then decreased. In the same period (January 2003 - December 2004), the prevalence per trimester of paroxetine

prescriptions decreased slightly from 2 per 10,000 to 1.5 per 10,000, with a statistically significant trend ( $\chi^2_t = 12.6$ ; d.f.=7;  $p < 0.001$ ), and the incidence per trimester decreased from 1 per 10,000 to 0.8 per 10,000 ( $\chi^2_t = 6.4$ ; d.f.=7;  $p = 0.01$ ).

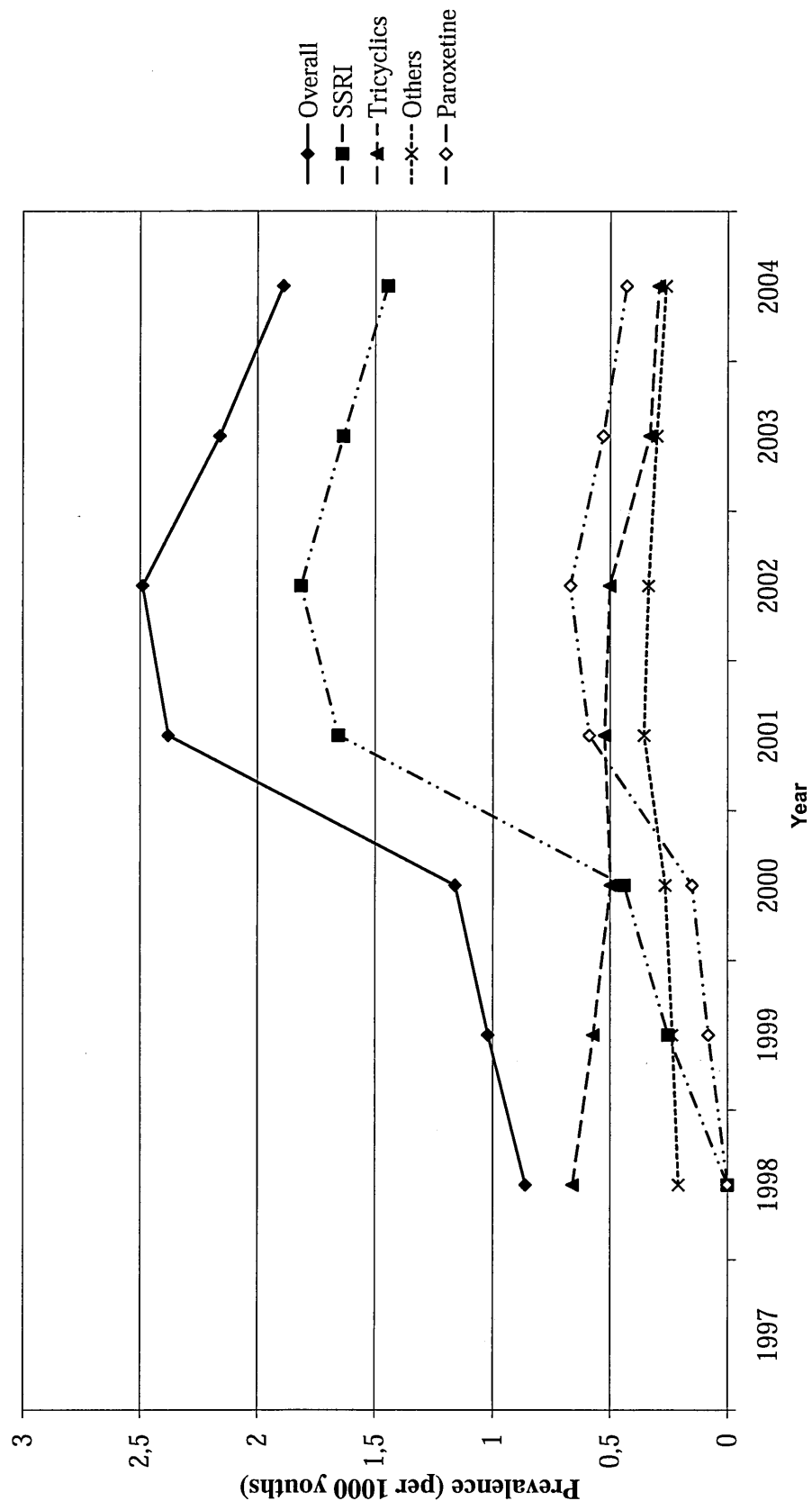
A total of 926 children and adolescents received a psychotropic drug prescription during 2004 for the first time; 808 were new antidepressant users and 143 new antipsychotic users. A total of 566 youths received the first antidepressant prescription during the first six months of 2004, 349 of which (62%) did not receive further prescriptions in the following 6 months.

**Table 18 – Prevalence and incidence of psychotropic drug prescription in children < 18 years, 1998 to 2004. Values are expressed as: users per 1000 residents <18 years; (number of children).**

	1998 N= 537,901	1999 N=536,797	2000 N=535,820	2001 N=537,958	2002 541,903	2003 N=565,619	2004 N=574,834
<b>Antidepressants</b>							
Prevalence *		1.02 (548)	1.16 (624)	2.38 (1278)	2.49 (1349)	2.16 (1224)	1.89 (1086)
Incidence *	0.86 (463)	0.88 ( 470)	0.98 (522)	2.10 (1128)	1.95 (1055)	1.67 (943)	1.41 (808)
<b>Antipsychotics</b>							
Prevalence		0.62 (333)	0.63 (337)	0.83 (449)	0.74 (399)	0.56 (319)	0.53 (306)
Incidence *	0.63 (339)	0.40 (214)	0.42 (223)	0.59 (317)	0.42 (226)	0.29 (162)	0.25 (143)
<b>Lithium</b>							
Prevalence		0.03 (15)	0.03 (15)	0.05 (26)	0.06 (30)	0.07 (40)	0.04 (24)
Incidence <sup>†</sup>	0.04 (20)	0.01 (8)	0.02 (11)	0.04 (21)	0.03 (16)	0.04 (24)	0.03 (19)
<b>Any</b>							
<b>psychotropic</b>							
Prevalence *		1.60 (857)	1.75 (938)	3.02 (1626)	3.08 (1668)	2.63 (1488)	2.32 (1335)
Incidence *	1.46 (788)	1.25 (669)	1.38 (737)	2.57 (1382)	2.31 (1246)	1.93 (1088)	1.62 (926)

\* significant trend with p<0.0001; <sup>†</sup> p=0.02

Figure 13 - Trend of prevalence (per 1000 youths) of antidepressant prescription in children < 18 years, 1998 to 2004.





A total of 112 children and adolescents (8% of those receiving psychotropic drugs in 2004) had been treated for at least 3 years. There was a statistically significant difference in chronically treated youths between antipsychotic and antidepressant users (20.6% versus 5.5% respectively;  $\chi^2 = 55$ , d.f.=1;  $p < 0.0001$ ). The prevalence of chronic therapy was also higher in boys than in girls (10.9% versus 5.8%;  $\chi^2 = 11.2$ , d.f.=1,  $p = 0.0008$ ) and there was no statistically significant difference between adolescents and school age children (9.2% versus 8.7%;  $\chi^2 = 0.11$ , d.f.=1;  $p = 0.74$ ).

During the 3 year observation period, the patients received a total of 28 different drugs (14 antidepressants, 13 antipsychotics, and lithium), each patient received an average of 2.3 drugs (range 1-10) and an average of 61.5 boxes (range 10-752); 36 children and adolescents received three or more psychotropic drugs. Risperidone was the most prescribed drug to chronically treated youths: during 2004 it was prescribed to 30 children, 22 of which were treated with this drug for the entire 3 year period. Sertraline was the most prescribed antidepressant (19 children), followed by paroxetine (13 children). The percentage of chronically treated youths did not differ between SSRI and tricyclic users (5.9% versus 3.6%, respectively).

The drug with the highest rate of chronically treated users was periciazine: 8 of the 21 patients receiving periciazine during 2004 had been in treatment with this drug for at least 3 years.

A total of 45 patients (24 antipsychotic users, 20 antidepressant users and one child treated with lithium) did not change the therapy during the 3 years; 13 youths were prescribed risperidone.

#### 4. Discussion

This was the first study to evaluate the prevalence of psychotropic drug prescriptions in the Italian pediatric population and, considering the sample size, it is also the largest epidemiological study ever performed on this topic.

Some limitations should be considered in interpreting the findings of this study.

First of all, only prescriptions of drugs reimbursed by the National Health Service could be analyzed, so the prevalence of psychotropic drug utilization may be underestimated (e.g. anxiolytic prescriptions were not evaluated). For the same reason, it is not possible to evaluate SSRI prescriptions before 1999, since they were not reimbursed by the National Health Service. However, an increase in prescribing was observed also in evaluating the wholesale data,<sup>103</sup> so it is likely that, before 1999, SSRI prescriptions were almost negligible.

Moreover, the ARNO database does not collect information concerning the diseases for which drugs are administered, so only assumptions on the prevalence of psychiatric disorders or the appropriateness of the therapies could be made.

Basing on the findings of this study, the number of Italian children and adolescents currently receiving a psychotropic medication can be roughly estimated as being between 28,000 and 30,000; 23,600 of these receive antidepressant medication and nearly 6,800 receive antipsychotics. About 2000 Italian children or adolescents have been in treatment for at least three years.

Large differences were found in prevalence between LHUs. These may be due to differences in prevalence of neuropsychiatric disorders between setting, to socio-cultural or economic determinants or to different prescribing habits between physicians. However, it is interesting to note that the greatest value of prevalence was found in Tuscany region, where it is based one of the most prominent national centre for the treatment of child neuropsychiatric disorder.

The gender differences in prescription prevalence appear consistent with the epidemiology of the psychiatric disorders: antipsychotic drugs were more frequently prescribed to males and antidepressant medications to adolescent females. However, the school age male children received antidepressants more frequently compared to girls, suggesting that antidepressants were probably administered for obsessive compulsive disorders or attention deficit hyperactivity disorder (ADHD) as well, also taking into account that, in Italy, methylphenidate and atomoxetine are not on the market.

Even though the prevalence in Italy is substantially lower than that observed in United States (10%-20%), but with similar age and gender distributions, and is a half of that of other European Countries (3.7-6.0%), the rate of children treated with antidepressants, in particular with SSRIs, raises some concerns. To date, the available data on the safety and efficacy of these drugs in the pediatric population are limited. A meta-analysis of 12 RCTs, involving a total of 1,044 participants, on OCD treatment with fluoxetine, fluvoxamine, paroxetine and sertraline showed that SSRIs are more effective than placebo.<sup>104</sup> Although clomipramine was found to be more effective than SSRIs, according to the American Academy of Child and Adolescent Psychiatry, SSRIs could be considered first-line drugs because of their fewer side effects and lower toxicity with respect to clomipramine.<sup>105</sup> In such a context, the fact that clomipramine is among the 10 most prescribed psychotropic drugs in children below 5 years of age is a significant source of concern.

On the contrary, the efficacy of pharmacological therapies for MDD in children and adolescents is controversial.<sup>83</sup> A systematic review of the literature did not find a statistically significant difference between tricyclic antidepressants and placebo,<sup>106</sup> while taking SSRIs into account the risk-benefit profile appears favourable only for fluoxetine.<sup>107-109</sup>

The safety of antidepressant use in children is also debated, in particular regarding the SSRIs and the link with an increased risk of suicidality. In fact, an analysis of 24 placebo controlled trials showed a two-fold greater risk of suicidal behaviour in patients receiving antidepressants.<sup>82</sup>

Moreover, the incidence of some adverse events may differ between age: an analysis of adverse events reported in the RCTs comparing SSRIs and placebo found that activation and vomiting were more prevalent in children than in adolescents, and that their rate was lowest in adults. On the contrary, somnolence was an uncommon adverse event in children.<sup>110</sup>

Furthermore, the trials performed lasted between 8-12 weeks so scant data are available concerning the long-term safety period and little is known about the effects on neurologic and behavioural development. In this regard, some exploratory animal and human findings suggest that early life exposure to antidepressants may affect motor, cognitive and affective development.<sup>111-113</sup>

The SSRIs could also be linked with growth reduction, as suggested by some case-reports.<sup>114</sup>

The analysis of the prescribing pattern found that a total of 14 psychotropic drugs (11 antidepressants and 3 antipsychotics) could be sufficient to address the main therapeutic needs of children and adolescents independently of age (table 18); 6 of these drugs ranked among the first ten in order of prescription in all the age groups: 4 SSRIs (paroxetine, sertraline, citalopram, fluoxetine), venlafaxine and amitriptyline. In spite of this, the SSRIs licensed for use in children in Italy are sertraline and fluvoxamine for obsessive compulsive disorder (OCD), respectively, in children  $\geq 6$  years and  $\geq 8$  years, and fluoxetine for the treatment of depression in children  $\geq 8$  years, while amitriptyline is licensed in children  $> 12$  years of age.

Moreover, the prescribing pattern of antidepressants seems to not be based on the available safety and effectiveness evidence. The only SSRI with some evidence of efficacy in treating depression in children and adolescents is fluoxetine,<sup>115</sup> which is also the only SSRI licensed for the treatment of depression in the paediatric age, but it is prescribed in Italy to a lesser extent compared to paroxetine and citalopram.

Paroxetine was the most prescribed drug in adolescents. The data concerning efficacy in pediatric depression are scant. Three randomized placebo controlled trials were performed: two negative trials were published only in 2006,<sup>116,117</sup> after the company was accused of withholding data in order to overestimate the efficacy of the drug,<sup>118</sup> and in the third, the authors suggested a greater efficacy of paroxetine even though no statistically significant differences were found on the primary outcome measure.<sup>119</sup> On the contrary, the safety of this drug raises some concerns: paroxetine was the first SSRI for which a link with an increased risk of suicide was suspected, and, during the summer of 2003, several drug regulatory agencies (Medicines and Healthcare Regulatory Agency [MHRA] in the United Kingdom and Food and Drug Administration [FDA] in the United States first) warned health professionals about the risk of suicidal ideation linked to paroxetine. In August 2003, the Italian Ministry of Health issued a Dear Doctor Letter to emphasize the contraindications for use in childhood.

Citalopram was the second antidepressant in order of prescriptions in the adolescents, even though only one randomised controlled trial was published in 2004 and it did not provide sound evidence of efficacy.<sup>120</sup> Its enantiomer escitalopram, licensed in Italy in 2003, was among the most prescribed antidepressants despite the fact that no paediatric RCTs were published at that time. A negative RCT was published only in 2006.<sup>121</sup>

Moreover, also venlafaxine is among the most prescribed drugs. However, according to the review by the FDA, this drug is linked with the highest risk of suicidal ideation (RR

4.97, 95%IC 1.09-22.72).<sup>82</sup> On the contrary, the trials did not find statistically significant differences in depressive symptoms between venlafaxine and placebo.<sup>122</sup>

The prevalence trend shows an increase between 1998–2002, followed by a decrease; a quite similar pattern was observed in the UK and Ireland.<sup>69,74</sup> The reduction in antidepressant prescriptions between 2002 and 2004 could have been influenced by the regulatory agencies' resolutions and the debate on the medical journals. However, the finding that 80% of youths receiving antidepressants during 2004 were “new” users suggests that more effort should be made to raise physicians' awareness of the risks of prescribing antidepressants to young people. The same pattern was also observed for paroxetine, despite the Dear Doctor Letter issued by the Italian Ministry of Health.<sup>123</sup> The antidepressant prescriptions may also not be appropriate for treating depression, since 62% of people receiving an antidepressant prescription for the first time in the first semester (January-June) of 2004 did not receive any further drug prescriptions in the following six months, and the prescribed therapy could have barely covered the 8 week trial period needed for evaluating the treatment effects.<sup>124</sup>

Only 8% of children receiving psychotropic drug were chronically treated. According to this finding, it could be estimated that 2 per 10,000 youths have a severe psychiatric disorder, with a rate of 6 per 10,000 during adolescence.

The rate of chronic treatment was significantly higher in males treated with antipsychotics (21%), while nearly 6% of antidepressant users were chronic.

Risperidone was the most prescribed drug in chronically treated youths: 18% of children receiving this drug were treated for at least 3 years. Risperidone is an atypical neuroleptic licensed for disruptive behaviour treatment in children  $\geq 5$  years old, with a lower incidence of side effects (in particular tardive dyskinesia) compared to haloperidol. Some RCTs, enrolling a few hundred patients, found greater efficacy with

respect to placebo in improving symptoms in psychosis, disruptive behaviour, and autism,<sup>125,126</sup> but the long term efficacy is still debated.<sup>127</sup>

Moreover, even if the prevalence is low (3 per 100,000), periciazine is the psychotropic drug with the highest proportion of chronically exposed patients (38%) despite the scant evidence concerning its safety and effectiveness in the pediatric population (only one clinical trial evaluating safety and efficacy and of this drug in the pediatric population was retrieved in Medline and Embase<sup>128</sup>). Periciazine is licensed in Italy for the treatment of psychosis in children > 1 year old.

The increase in psychotropic drug use during the last few years in the northern countries of the world calls for data on the profile of the psychiatric disease rates in children and adolescents. Affordable diagnostic instruments are lacking, especially for the young population, and those available are not often used according to evidence based criteria.

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Such a context allows for other reasons and interests (those of the market) to influence the prescriptions, as with the well documented saga of psychotropic drugs in the adults over the last few decades.<sup>129</sup> Thus, the pediatric field, already submersed with antibiotics, respiratory drugs, and vaccines, can represent a fertile field also for invented or emphasized needs at which to push psychotropic drugs.

STEPS (Safety, Tolerability, Efficacy, Price, Simplicity) criteria for psychotropic drugs in the pediatric population need to be documented once again for the majority of the indications. In fact, this can be defined as an off-label drug subclass for children. To overcome this condition, independently funded collaborative trials should be planned to guarantee adequate (safe and effective) diagnostic and therapeutic care to children and their families with psychiatric or psychological diseases.

## **B.ANTI-ASTHMATIC DRUG PRESCRIPTION: A MODEL TO IDENTIFY POTENTIAL ASTHMA SUBJECTS**

### **1. Introduction**

Asthma is the most common chronic disease in childhood; in Italy its prevalence is estimated to be 9% in children 14 years of age or younger.<sup>130</sup> Asthma represents a huge burden for children, families and society.<sup>88,131</sup> Great attention is paid to therapeutic strategies that could prevent disease progression and international guidelines are available,<sup>132-134</sup> even if they are far from being routinely applied in clinical practice.<sup>64</sup>

In this context, anti-asthmatic drug prescriptions can represent an indicator for the quality of care.

An analysis of the prescription profile of anti-asthmatic drugs in a paediatric population was therefore performed with the aim to assess the feasibility of using prescriptions as potential markers of disease severity, and to evaluate adherence to international guidelines.

### **2. Methods**

All paediatric prescriptions dispensed by the retail pharmacies of the Local Health Unit of Lecco, Lombardy Region, between 1 January and 31 December 2003 were analysed.

The studied population was composed by 55,242 children under 18 years and represented 3.7% of the population  $\leq 17$  years of Region Lombardy.

Anti-asthmatics were classified as drugs belonging to the R03 main therapeutic group of the ATC classification (table 19).



Table 19 – List the of anti-asthmatic drugs (R03 main ATC group) available in Italy.

ATC 3 <sup>rd</sup> level	ATC 4 <sup>th</sup> level	Drug
Adrenergics, Inhalants (R03A)	Selective $\beta_2$ adrenoreceptor agonists (R03AC)	Salbutamol, terbutaline,
		fenoterol, formoterol, salmeterol;
	Adrenergics and other drugs for	Fenoterol+ipratropium;
		Salbutamol+beclometasone,
	obstructive airway diseases (R03AK)	salbutamol+flunisolide;
Other Drugs For Obstructive Airway	Glucocorticoids (R03BA)	salbutamol+ipratropium;
		salmeterol+fluticasone;
		beclometasone+formoterol,
		Formoterol+budesonide
		Beclometasone, budesonide, flunisolide,
Diseases, Inhalants (R03B)		fluticasone

	Anticholinergics (R03BB)	Ipratropium bromide, oxitropium bromide
	Antiallergic agents, excl. corticosteroids (R03BC)	Cromoglicic acid, nedocromil
	Adrenergics For Systemic Use (R03C)	
	α and β adrenoreceptor agonists (R03CA)	Ephedrine
	Selective β <sub>2</sub> adrenoreceptor agonists (R03CC)	Salbutamol, clenbuterol
	Xanthines (R03DA)	Aminophylline, bamifylline, diprophylline., doxofylline, theophylline.
	Leukotriene receptor antagonists (R03DC)	Montelukast, zafirlukast.
Other Systemic Drugs For Obstructive Airway Diseases (R03D)		

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In order to identify potential asthmatic patients, subjects  $\geq 6$  years of age were distributed in three groups based on number of boxes received during 2003: A) “occasional users”, subjects receiving only one box (i.e. a single course of therapy) ; B) “low users”, subjects receiving 2 or 3 packages; C) “high users”, subjects receiving 4 or more packages. The threshold of 4 packages was chosen because it represents the 90<sup>th</sup> percentile in distribution of frequency of treated children by number of packages. Prescription profiles (classes of anti-asthmatics, active principles, formulations, associations) were analysed in these three groups of subjects, taking prescriptions of short acting  $\beta_2$  adrenergic agonists (SABA) into special consideration. In order to evaluate whether these three groups permit the identification of disease severity, a few indicators were chosen: use of anti-asthmatics only in co-prescription with antibiotics (prescription of antibiotics  $\pm 7$  days from anti-asthmatic prescription); appropriate formulation (prescription of metered dose inhaler, MDI or dry powder inhaler, DPI); prescription of systemic steroids; and rate of hospitalisation for asthma (ICD IX = 493), considering hospital discharge forms (SDO).

Such indicators (the first two related to asthma, the others to disease severity) were used in a multinomial logistic regression analysis.

Multinomial regression model was estimated using as the dependent variable the degree of exposure to anti-asthmatic drugs, which was classified into three categories: occasional, low and high use.

The odds ratio and their confidence intervals were estimated using the “occasional” category as reference, adjusting for the age and gender.

In the regression analysis were included the following independent variables: use of age-appropriate formulation; exclusive antibiotic+anti-asthmatic co-prescription;

systemic steroid prescription; hospitalisation for asthma. The interaction between variables were not taken into account.

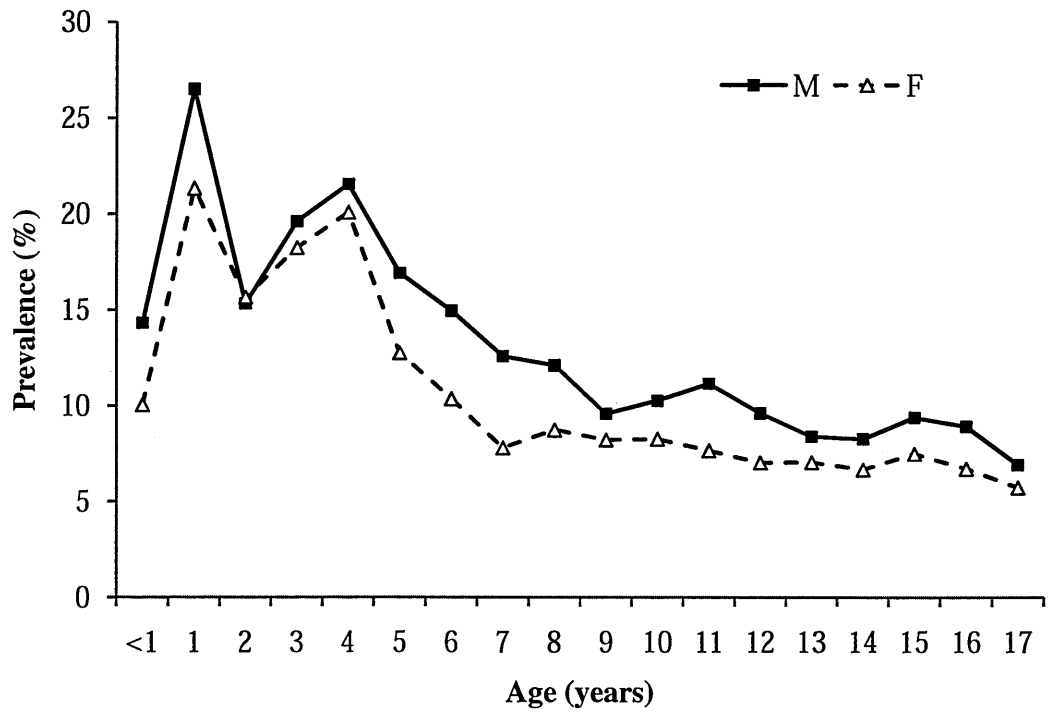
### **3. Results**

#### *a) Prescription profile in the $\leq 17$ years old population*

In all, 24,407 children and adolescents (44% of the studied population) received at least one drug prescription, and 6,594 of them (27% of those treated) received at least one anti-asthmatic drug. In 74% of cases the prescription was written by the paediatrician. A total of 23 anti-asthmatic drugs were prescribed, corresponding to 13,276 drug packages. Every treated child received a median of 2 packages (min 1, max 39). The average anti-asthmatic prescription prevalence was 12%, with two age-dependent peaks at 1 and 4 years (Figure 14).

Overall prevalence of anti-asthmatics was 1.24 fold higher in boys than in girls.

**Figure 14 - Trend of prevalence (%) of anti-asthmatic prescription in children and adolescents <18 years.**



Inhaled steroids were the more frequently prescribed anti-asthmatics (84% of those treated), while 33% of those treated received an adrenergic agonist. Altogether, these two classes represent 89% of dispensed boxes and their prevalence trend by gender and age is similar to the overall trend of anti-asthmatics. Beclomethasone was the most prescribed anti-asthmatic (58%), followed by salbutamol (31%), and salbutamol in fixed combination with other anti-asthmatic (13%). The first ten anti-asthmatics in terms of prescription represent 97% of the total of dispensed boxes. A total of 96% of prescriptions concerned inhaled formulations, and  $\frac{3}{4}$  of these were nebulised solutions/suspensions. Flunisolide and beclometasone were dispensed almost exclusively in a nebulised formulation (99 and 98% of the boxes, respectively). Salbutamol was prescribed in 74% of the cases as nebulised formulation.

58% of children treated with anti-asthmatics received only one package, 26% 2 packages, 7% 3 packages, and 11% 4 or more packages. In all, 61% received only one drug, mainly beclometasone (37%); 27% received 2 drugs (12% salbutamol+beclometasone), and 13% received 3 or more drugs. 42% of the anti-asthmatic prescriptions were associated with an antibiotic. A total of 1,789 children (27%) received an anti-asthmatic co-prescribed exclusively with an antibiotic.

#### *b) Prescription profile of preschoolers*

A total of 3,265 children <6 years (18%) received at least one prescription of anti-asthmatic drug. 1,741 (53%) received only one box, and 305 (9.3%) 4 or more boxes. In all, 853 children (26%) received exclusively antibiotic-anti-asthmatic co-prescription and 3,040 (93%) only nebulised formulations only. The most prescribed drugs were beclometasone (13.3%), salbutamol (7.7%) and flunisolide (2.7%).

#### *c) Estimation of asthma prevalence and disease severity*

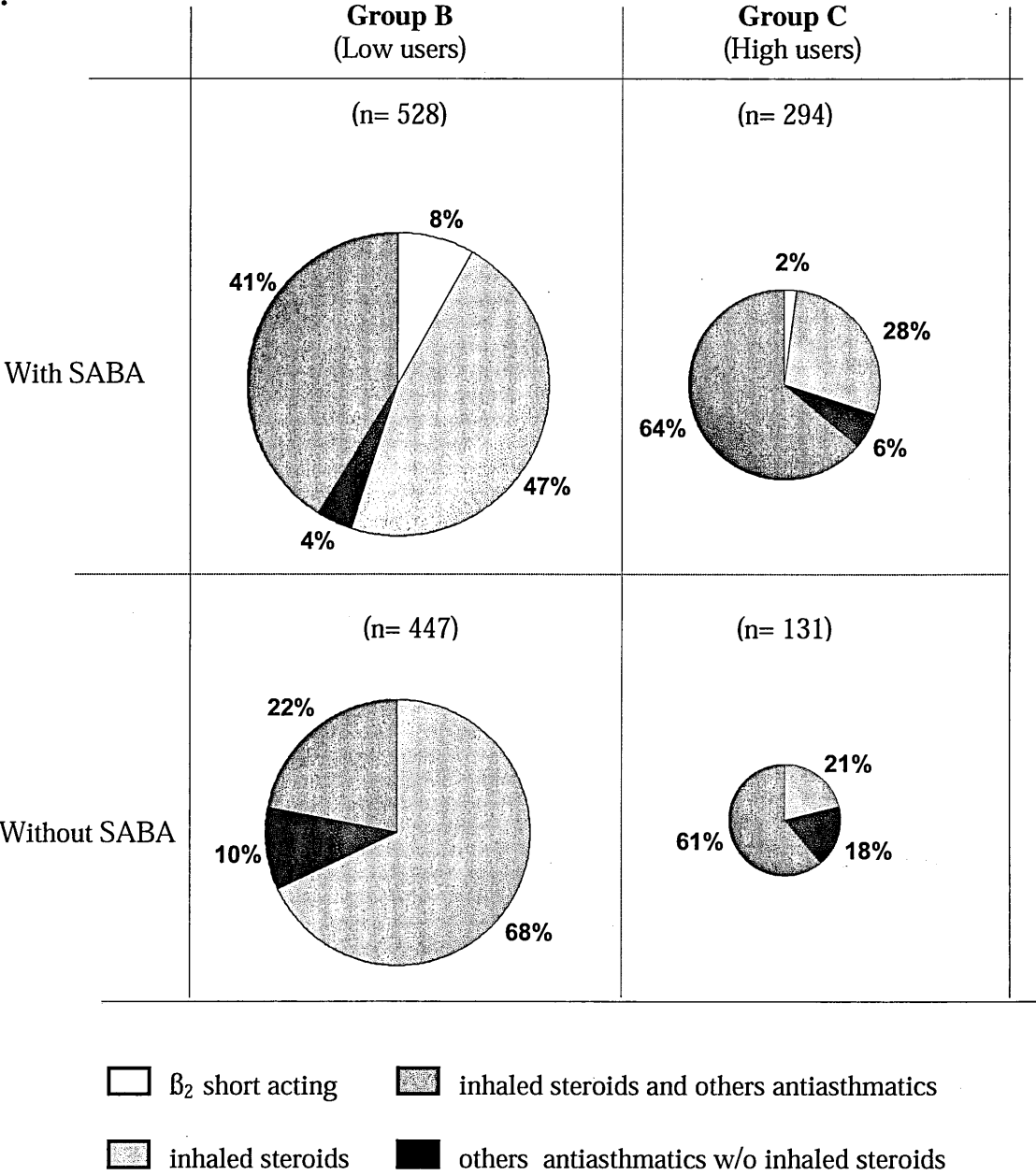
A total of 3,329 children and adolescents (9.0%) between 6 and 17 years of age received at least one anti-asthmatic drug prescription. 58% of children treated with an anti-asthmatic received only 1 package (group A), 29% received 2 or 3 packages (group B), and 13% received 4 or more packages (group C). Beclometasone and flunisolide were mainly prescribed in a occasional manner (group A) while, on the contrary, 70% of children treated with montelukast belonged to group C. Beclometasone was the most prescribed drug in group A (55% ) and B (49%), almost exclusively as a nebulised suspension (97% of prescribed boxes), and salbutamol was the most prescribed in group C (51%). In all, 1,435 subjects  $\geq 6$  of age received at least one prescription of  $\beta_2$  adrenergics; 1213 received SABA (719 of which received MDI and DPI formulations) and 363 long acting  $\beta_2$  adrenergic agonists. The prevalence of prescriptions of SABA

ranged from 19% in group A to 69% in group C, with significantly different rates between A and B ( $\chi^2=13$ ; d.f.=1;  $p<0.001$ ) and between B and C ( $\chi^2=29$ ; d.f.=1;  $p<<0.001$ ).

Figure 15 compares the distribution of drug classes in group B (low users) and C (high users), stratified by prescription of short acting  $\beta_2$  adrenergics. In all, 8% of group B and 2% of group C received only short acting  $\beta_2$  adrenergic agonists. Among the low users, SABA were prescribed mainly with steroids (47%), while nearly 2/3 of high users treated with SABA also received steroids and LABA. Inhaled steroids alone represent the more frequent therapeutic profile in group B (31% of low users). In all, 5% of subjects in groups B and C received neither a prescription for acute attacks (SABA) nor for maintenance therapy (steroids). In particular, 34 subjects had antileukotrienes, 27 cromons and 8 salmeterol.

34% of group B were in monotherapy (one drug only), in particular 16% with beclometasone and 4% with flunisolide or salbutamol, versus 11% of group C (montelukast or beclometasone to 3% of subjects, each). In all, 62% of group C received prescriptions of 3 or more drugs compared to 23% of group B.

**Figure 15 - Prescription profile of anti-asthmatics by class of drugs, stratified by prescription of short acting  $\beta_2$  adrenergics (SABA)**





#### d) Hospitalisation

In all, 3,906 subjects underwent hospitalisation (7% of the studied population).

Asthma was the cause of hospitalisation in 86 children. Among children treated with antiasthmatic drugs, 689 (10%) underwent hospitalisation and 76 (1%) of these because of asthma. Among children older than 6 years of age, 170 (5%) were hospitalised and, of these, 21 (0.6%) were hospitalised for asthma.

**Table 20 - Odds ratios from logistic regression analysis of anti-asthmatic users**

	N(%)	OR # (CI 95%)
<i>Age appropriate formulation</i>		
<i>(MDI and PDI)</i>		
A	398 (21%)	-
B	441 (45%)	3.2 (2.69-3.86)*
C	352 (83%)	18.4 (13.67-24.76)*
<i>Exclusive Antibiotic co-prescription</i>		
A	758 (39%)	-
B	171 (18%)	0.5 (0.38-0.55)*
C	20 (5%)	0.1 (0.09-0.22)*
<i>Systemic steroids</i>		
A	27 (1.4%)	-
B	25 (2.6%)	2.4 (1.33-4.27)†
C	32 (7.5%)	8.6 (4.47-16.66)*
<i>Hospitalisation for asthma</i>		
A	3 (0.2%)	-
B	4 (0.4%)	1.6 (0.32-8.26)
C	14 (3.3%)	6.8 (1.48-31.42) †

\* p<0.0001    †p<0.05    # adjusted Odds Ratio controlled for gender and age

#### *e) Multivariate analysis*

Table 20 reports the differences between the three groups of subjects resulting from a multinomial multivariate logistic regression analysis adjusted for sex and age.

Considering MDI and PDI (and not nebulised formulations) as appropriate for asthma therapy, exclusive antibiotic anti-asthmatic co-prescription, and systemic steroid prescriptions, significant differences were found in terms of OR between groups.

Furthermore, a significant difference was observed in hospitalisation rate for asthma between C and B versus A. On the contrary, no differences were found in the three groups for rate of hospitalisation for reasons other than asthma. The concomitant presence of two or more of these indicators was more frequent in group C than in B or A. In group C, all children were positive for at least two indicators, 10% for three and 0.9% for all four indicators.

### **4. Discussion**

#### *a) Estimation of asthma prevalence*

The anti-asthmatic prescription pattern observed in this study appears to be consistent with previous Italian reports. Although the Digitare l'equazione qui.prevalence is lower than in other Italian contexts, the trend is similar, with the highest values observed in preschool age. A total of 58% of children was treated with only 1 package of anti-asthmatics, in particular with nebulised beclometasone (which can cover 10 days treatment), suggesting that more than half of treated children received anti-asthmatics for acute diseases different from asthma, i.e. respiratory airway infections. This hypothesis is consistent with two findings. The first was that the highest prevalence values were estimated in preschoolers. More specifically, two peaks were observed, for both boys and girls, at 12 months (when defenses from maternal antibodies decrease) and 4 years (at the time of entry into the community). In particular the peak in the

second year of life, consistent with previous finding, strongly suggests the hypothesis that anti-asthmatics are mainly used in viral wheezing. The second was that 42% of anti-asthmatics were co-prescribed with antibiotics.

It should be underlined, however, that also 47% of the youths over 6 years old, in which occurrence of viral wheezing is less frequent, received occasional prescriptions of nebulised formulations. This data suggest that anti-asthmatics (especially beclometasone) are prescribed for respiratory airway infections also in the absence of bronchospasm, as described in other studies.<sup>100,135</sup> The overuse of beclometasone could be in part due to the fact that in Italy this drug is also licensed for rhinopharyngitis. The lack of information on diagnosis, a major limit of studies based on prescription databases, does not permit the identification of real asthmatic patients. In order to overcome this fault, a few criteria were chosen with the aim to identify potentially asthmatic subjects. The first was age  $\geq 6$  years; only in school-aged children it is, in fact, possible to discriminate between asthma and recurrent viral wheezing in a reliable manner.<sup>99</sup> The other criteria was based on drug consumption, using the number of boxes dispensed as an indicator. In this regard, occasional treatment (prescription of one package only) was an exclusion criteria, because it is related to conditions others than asthma, or to exercise-induced or intermittent asthma.

Using these criteria, a 3.8% asthma prevalence was estimated. This prevalence is inferior to that estimated by the SIDRIA survey (9.0% and 4.5% with persistent asthma).<sup>130</sup>

It is possible that the prevalence of asthma was overestimated in the SIDRIA survey. The reliability of self-reported asthma or asthma-like symptoms as a measure of asthma prevalence is in fact questionable.<sup>136,137</sup>

On the contrary, the model used in this study could be biased because of the arbitrariness of the chosen criteria. The 6-year age cut-off could exclude pre-schoolers

with asthma. Moreover, among occasionally treated subjects, 290 (15%) received adequate formulations (MDI and DPI) of  $\beta_2$  agonists and they could represent false negatives. On the other hand, 278 subjects classified as potentially asthmatic (groups B and C) received nebulised steroid prescriptions only, therefore they could represent false positives (26 and 5%, respectively, for groups B and C).

However, a specificity of 0.86 and a sensitivity of 0.63 in identifying asthmatic patients were reported in a study in which similar criteria were used: subjects  $\geq 6$  years receiving all classes of anti-asthmatics, excluding those who received only one prescription of steroids or  $\beta_2$  agonists.<sup>66</sup> Another study using age and number of prescriptions as inclusion criteria reports anti-asthmatic prescriptions in 7.5% of Dutch children only 4.1% of whom were later diagnosed as asthmatic.<sup>63</sup>

In order to increase specificity and sensitivity, an alternative model could be applied using two inclusion criteria in addition to age  $\geq 6$  years: the prescription of 4 or more boxes/year or at least one prescription of a  $\beta_2$  adrenergic agonist in MDI/DPI formulation. On the basis of these criteria 1,057 potentially asthmatic patients would be identified, corresponding to a asthma prevalence of 2.9%. According to the prescription data, a prevalence ranging between 3 and 4% would therefore be estimated. This is quite similar to those estimated in two studies based on prescription databases: 2.6% in Denmark and 5.4% in Norway.<sup>61,66</sup> It is likely that this estimate is more accurate than the one reported in the SIDRIA survey, but it is also possible that an underestimation exists. In fact, some asthmatic children may have purchased drug prescriptions in the previous year, while other asthmatic children may have not received drug therapy.

#### *b) Estimation of disease severity*

The aim of the study was also to try to estimate disease severity. In this regard, a threshold of 4 boxes was identified to categorise high and low users.

The hypothesis that groups B and C may represent different degrees of severity is supported by the different profiles of anti-asthmatic drug prescriptions, as well as by the results of the multivariate analysis.

Group C, compared to B, is characterised by: a higher rate of short acting  $\beta_2$  adrenergic agonist use (69 versus 54%); a higher number of subjects receiving multidrug therapy (62% of group C received 3 or more drugs versus 22% of B); and different associations of classes, for instance 46% of group C received SABA, LABA and steroids (an association suggested by guidelines for moderate-severe persistent asthma) compared to only 22% of group B. Furthermore, group C was characterised by a more frequent use of appropriate formulations (MDI and DPI) and by a very small percentage of children receiving anti-asthmatics only in co-prescription with antibiotics. The different prevalence of systemic steroids use between group B and C, as well as the difference in hospitalisation rates, also suggest that high users have a more severe underlying disease. Comparing these prescription patterns with international guidelines, it appears likely that group B (low users) would identify patients with mild persistent asthma, while group C (high users) would identify most of those with moderate-severe persistent asthma.

### *c) Appropriateness of the therapies*

Even if the validity of indicators of prescription versus clinical data in the assessment of the quality of asthma treatments is debated,<sup>138</sup> a few inadequacies were evident in prescriptions that did not follow the guideline recommendations. First of all, the wide use of nebulised suspension/solutions: 55% of group B and 17% of group C received this formulation exclusively, even if it is considered appropriate only for children under 5 years of age, when MDI with a spacer device is not clinically effective.<sup>139</sup>

Another possible inappropriateness, which regards 4 out of 10 potentially asthmatic patients, may be the prescriptions of inhaled steroids, or steroids +LABA without SABA. However, this is a cross sectional study and no data are available on the drug use during the previous years, thus it is not possible to discriminate between inadequacy or rather an optimal disease control, that do not require acute attack therapy. 10% of high users did not receive steroids (first choice anti inflammatory maintenance therapy) and 6% did not receive SABA. A total of 7 high user patients received SABA alone, either because not adequately treated or because experiencing intermittent asthma.

A very small percentage of subjects received a therapy with neither SABA nor steroids (5% and 6% groups B and C, respectively). Considering groups B and C together, 58% of antileukotrienes and 9% of LABA were prescribed without steroids. LABA alone would lead to a loss of disease control; in particular, salmeterol has been associated to deaths for respiratory failure.<sup>140,141</sup> Nearly all subjects treated with antileukotrienes + steroids belonged to group C.

The lack of information on the prescribed dose does not permit a more accurate evaluation of treatment appropriateness. This could be important, especially for steroids, for which the guidelines recommend an association with another anti-asthmatic instead of an increase in inhaled steroid dose.<sup>132,133</sup>

Despite some limitations, however, the model applied in this pilot study, by excluding occasionally treated group, appears to be valuable in identifying potentially asthmatic patients and, in particular, in estimating disease severity. However, this model needs to be validated by obtaining the therapeutic indication from the prescribers.

## **IX. THE ROLE OF PRESCRIBERS**

## **A. INTRODUCTORY NOTES**

Drug utilization studies performed in the Italian paediatric population found a prescription profile that appears country specific, in particular concerning antibiotics and anti-asthmatic use, for which quantitative and qualitative differences with other European countries were found. These differences may be due to several factors (e.g healthcare system, drug regulation, socio-cultural and economic determinants). It is likely that the different prescribing attitude between physicians may play a role in explaining the above differences.

The studies presented below were performed with the aim to evaluate the role of the prescribers (in particular the type of physician) in determining different profiles of drug prescription.

## **B. AN ESSENTIAL DRUG LIST FOR PRESCRIBING IN PRIMARY CARE (BASED ON THE PRESCRIBING ATTITUDES) OF FAMILY PAEDIATRICIANS.**

### **1. Introduction**

As reported in the previous chapters, a large number of drugs was prescribed to Italian children and adolescents.

It is likely that the high number of drugs is related to different prescribing habits between physicians. In this regard, it could be of interest to evaluate what the consensus between family paediatricians is concerning the drugs they need to prescribe, with the aim to create a list of essential medicines based on the prescribing attitudes of physicians.

According to the World Health Organization (WHO), essential medicines are those that satisfy the priority health care needs of the population. Essential medicines are selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative



cost-effectiveness. In selecting essential medicines, unnecessary duplication of drugs and dosage forms should be avoided.<sup>142</sup>

An analysis of data collected in a regional prescription database was therefore performed with the aim to identify the drugs for which a high degree of concordance exists between family.

The aim of the study was to identify the drugs for which a high degree of concordance exists between family paediatricians.

## **2. Methods**

The analysis involved prescriptions dispensed between 1 January and 31 December 2005 to 1,291,197 children and adolescents under 14 years of age living in the Lombardy Region (15.7% of the Italian population).

In order to collect homogeneous sample, family paediatricians below the 5-centile of the distribution of family paediatricians by number of treated children were excluded.

Since the differences between paediatricians concerning the number of children they were in charge of may influence the prescribing pattern, a second analysis was performed in a more homogeneous sample of paediatricians. In this second analysis, paediatricians were selected on the basis of interquartile range of the distribution of paediatricians by number of children they were in charge of.

A linear regression analysis was performed to evaluate the association between the number of drugs prescribed by each paediatrician and his/her gender and the number of children he/she had in charge.

The percentage of family paediatricians who prescribed each single drug was calculated and a percentage  $\geq 75\%$  was considered a high degree of concordance.

The relation between the degree of concordance and the prevalence or the percentage of packages was investigated using the non-parametric Spearman Rank Correlation test.

### 3 Results

During 2005, in the Lombardy Region there were 1165 family paediatricians, 58 of whom were excluded because they prescribed drugs to less than 84 children (5-centile) during the study period.

A total number of 1107 family paediatricians, who had in charge 923,177 children <14 years old, was selected. The median number of children per paediatrician was 832 (range 132-1452; interquartile range 636-991). In all, 486,406 (52.7%) children received drug prescriptions.

A total of 746 different drugs were prescribed (61% of those prescribed during 2005 to Lombardy's population). The median number of drugs prescribed by each paediatrician was 60 (range 19-189; interquartile range 51-71).

The number of drugs prescribed by the paediatrician increased with the number of children in charge ( $p < 0.0001$ ). On the contrary, the number of drugs did not differ between male and female paediatricians.

Table 21 reports the distribution of the number of drugs per percentage of paediatricians who prescribed them during 2005. In all, 92% of drug were prescribed by less than 25% of the family paediatricians. All drugs belonging to any of 56 therapeutic classes (79% of the total) were commonly to only less than  $\frac{1}{4}$  of the family paediatricians.

**Table 21 – Distribution of the number of drugs per degree of concordance (% of paediatricians who prescribed them)**

	<b>&lt;25%</b>	<b>25-49%</b>	<b>50-74%</b>	<b>≥75%</b>	<b>Total</b>
<b>N. Drugs</b>	683	21	20	22	<b>746</b>
<b>N. Therapeutic classes</b>	70	15	11	5	<b>71</b>
<b>N. antibiotics</b>	49	2	4	11	<b>66</b>
<b>N. antiasthmatics</b>	13	4	1	7	<b>25</b>
<b>N. antihistamines</b>	5	0	4	2	<b>11</b>
<b>N. antivirals</b>	6	0	0	1	<b>7</b>
<b>N. anticonvulsants</b>	16	2	0	1	<b>19</b>
<b>Others</b>	594	13	11	0	<b>618</b>

Twenty-two drugs were prescribed by at least 75% of family paediatricians (table 22). Six drugs were prescribed by all the family paediatricians (amoxicillin+clavulanic acid, amoxicillin, beclometasone, clarithromycin, salbutamol, and cefaclor), while 15 were prescribed by more than 95% of the family paediatricians.

During 2005 a total of 1015 out of 1107 family paediatricians (92%) prescribed during 2005 all four inhaled steroids marketed in Italy, while 95% prescribed the four leading cephalosporins (cefaclor, cefixime, ceftibuten and cefpodoxime).

In all, 1103 family paediatricians (99.6%) prescribed generic amoxicillin at least once and 1029 (93.0%) did so for generic cefaclor.

**Table 22 – The 22 drugs prescribed by at least 75% of the paediatricians**

<b>Drug</b>	<b>Paediatricians (% )</b>	<b>Prevalence (%)</b>	<b>Packages (%)</b>	<b>Expenditure (%)</b>
<b>Amoxicillin+clavulanic acid</b>	100.0	21.4 (1)*	22.5 (1)*	15.6
<b>Amoxicillin</b>	100.0	16.4 (2)	15.5 (2)	2.9
Beclometasone	100.0	11.3 (3)	6.7(3)	5.1
<b>Salbutamol</b>	100.0	8.1 (4)	4.8(6)	1.4
Clarithromycin	100.0	7.8 (5)	5.5 (5)	9.5
Cefaclor	100.0	7.1 (6)	6.4 (4)	3.6
<b>Azithromycin</b>	99.9	5.4 (7)	3.5 (7)	4.5
Cefixime	99.9	3.9 (8)	2.7 (8)	3.4
Cetirizine	99.6	2.2 (12)	1.9 (12)	1.4
Ceftibuten	99.1	2.8 (9)	1.9 (10)	2.8
<b>Aciclovir</b>	98.4	1.4 (15)	0.8 (19)	0.8
Flunisolide	97.9	2.2 (11)	1.2 (15)	1.7
Fluticasone	97.3	1.4 (13)	1.2 (16)	1.3
Cefpodoxime	96.2	2.3 (10)	2.0 (9)	1.8
<b>Budesonide</b>	95.5	1.4 (14)	0.9 (17)	1.2
Oxatomide	93.9	1.1 (16)	0.6 (23)	0.2
Salmeterol+fluticasone	87.5	0.5 (21)	0.6 (21)	1.7
Montelukast	87.0	0.5 (22)	0.9 (18)	2.5
<b>Ceftriaxone</b>	86.6	0.8 (19)	1.9 (11)	0.7
<b>Valproic acid</b>	80.8	0.3 (33)	1.7 (13)	0.6
Cefuroxime	78.9	0.9 (17)	0.7 (20)	0.6
Cefprozil	77.1	0.6 (20)	0.5 (26)	0.4

\* ( ) rank of overall prescription. The drugs listed in the *WHO Model List of Essential Medicines for Children* are reported in bold.

The 22 drugs with a degree of concordance  $\geq 75\%$  were also the most prescribed to the paediatric population of Lombardy Region and covered 96% of the treated children, 84% of the dispensed packages, and 64% of the expenditure. (Table 22)

For these drugs, a statistically significant correlation between rank distributions of the degree of concordance, the prevalence ( $r_s=0.94$ ; d.f.=20;  $p < 0.001$ ), and the percentage of packages ( $r_s=0.85$ ; d.f.=20;  $p < 0.001$ ) was found.

For the second step of the analysis, paediatricians who cared for by 636- 991 children (interquartile range of the distribution of paediatricians by number of children in charge) were selected and the degree of agreement for each prescribed drug was estimated.

These paediatricians prescribed a total number of 657 drugs, and the median number of drugs prescribed by each paediatrician was 61 (interquartile range 54-70). The drugs with a degree of agreement  $\geq 75\%$  were 24: those previously identified and reported in table 22, with phosphomycin and prednisone.

## 4 Discussion

This is the first study analysing the concordance between family paediatricians on drug prescriptions. In this regard, the evaluation of the prescribing pattern can identify which drugs the family paediatricians really need in their daily practice.

A concordance between at least 75% of the family paediatricians, was found only for 22 out of 746 drugs (3%) and the number increased to 42 when a 50% degree of concordance was considered.

This figure did not change after selecting paediatricians who care for by a quite similar number of children.

On the contrary, 92% of drugs were prescribed by less than 25% of family paediatricians. A high percentage of drugs shared by less than 25% of family paediatricians was observed also in the most prescribed therapeutic classes. For example, 74% of antibiotics were prescribed by less than  $\frac{1}{4}$  of family paediatricians.

Moreover, it is interesting to note that during the study period family paediatricians prescribed a median number of 60 drugs: nearly 3-fold the number of drugs for which a high degree of concordance was found.

These data therefore confirm that a plethora of me too drugs (i.e. drugs structurally very similar, with only minor pharmacological differences between them) were prescribed in Italy.

Moreover, the essential list developed on the basis of drugs shared by at least  $\frac{3}{4}$  of family paediatricians is redundant. In fact, 12 antibiotics, 7 of which were cephalosporins, and 6 anti-asthmatics were included. At the same time, however, this list may be insufficient to cover the health needs, since only a few therapeutic classes were incorporated.

The World Health Organization (WHO) criteria for identifying essential medicines take into consideration disease prevalence, evidence on efficacy and safety, and comparative

cost-effectiveness. In selecting essential medicines, WHO underlines that unnecessary duplication of drugs and dosage forms should be avoided.<sup>142</sup>

Moreover, according to the WHO *Guide to good prescribing*, physicians should choose their personal drugs on the basis of efficacy, safety, suitability, and cost.<sup>143</sup>

In this regard, it is interesting to note that 95% of the family paediatricians had at least four cephalosporins (cefaclor, cefixime, ceftibuten, and cefpodoxime) in their personal formularies. At this point one is led to the question whether these drugs are equivalent in terms of efficacy, safety, suitability, and cost. Cefixime and ceftibuten, which ranked 8<sup>th</sup> and 9<sup>th</sup> in descending order of prevalence, are a clear example of duplication of drugs, since they are two third-generation cephalosporins with the same dosage schedule (once daily).

The duplication of drugs is associated with increased expenditure. In fact, a total of 1.7 million euros (5% of the total expenditure) would be saved if cefaclor was chosen instead of the other three cephalosporins.

Moreover, cephalosporins are widely used in Italy, but they are rarely prescribed to outpatient children in northern European countries.<sup>97</sup> It is therefore odd that a very high percentage of family paediatricians prescribed four different cephalosporins each: one second and three third generation drugs. International guidelines concerning the treatment of the most common childhood infections (acute otitis media, pharyngotonsillitis, and sinusitis) consider cephalosporins a second-choice therapy and state that, when needed, a first generation cephalosporin should be preferred.<sup>90-93</sup>

Only 3 of the 16 prescribed cephalosporins were first-generation, and cefalexin, the only oral cephalosporin included in the WHO List of Essential Medicines for Children,<sup>14</sup> was shared by only 13% of the family paediatricians.

At the same time, during 2005, 92% of the family paediatricians prescribed all the four inhaled steroids marketed in Italy.

In part, this profile may be influenced by specialists' prescriptions for asthma and it is likely that some children may be in therapy with budesonide and others with fluticasone. However, beclometasone and flunisolide are almost exclusively prescribed in Italy as a nebulised suspension for the treatment of upper respiratory tract infections, without evidence of efficacy.<sup>100</sup> It is therefore difficult to understand why some patients would need flunisolide and others would need beclometasone.

The 22 shared drugs, with the exception of ceftibuten and oxatomide, are included in the British National Formulary for children (BNF-C). However, the redundancy of this list of drugs is highlighted also by the finding that only 8 out of the 22 drugs were included in the WHO Model List of Essential Medicines for Children.<sup>144</sup>

This study has some limitations. First of all, data concerning drugs without state reimbursement are lacking and it is therefore likely that the number of drugs shared by family paediatricians is higher. However, the findings from a study involving 35 family paediatricians suggest that only for a few not reimbursed drugs (mainly paracetamol and domperidone) is a high concordance between family paediatricians likely to be observed.<sup>29</sup>

Moreover, only family paediatricians in the Lombardy Region were involved and it is likely that, at the national level, the list of drugs prescribed by 75% or more family paediatricians is slightly different. However, drug prescription profile reported in this study is similar to that observed in other national settings and the 22 drugs shared by 75% or more family paediatricians are the most prescribed drugs also in other Italian regions.

This study should be replicated at the national and multinational levels to identify drugs for which a consensus exists between family paediatricians. In this regard, it is interesting to note that a multinational cohort study evaluating drug prescriptions given to children in the UK, the Netherlands and Italy reported a different prescribing profile



at country level and found that only salbutamol was among the 10 most prescribed drugs in all the three countries.<sup>32</sup> Identifying shared drugs may therefore be useful in creating a practice based international formulary.<sup>145</sup>

## **C. DIFFERENCES IN THE DRUG PRESCRIPTION TO CHILDREN BY ITALIAN PEDIATRICIANS AND GENERAL PRACTITIONERS.**

### **1. Introduction**

According to some international studies, drug prescriptions are influenced by the type of physician writing them. In fact, differences in prescription profiles between family paediatricians and general practitioners were found, in particular concerning antibiotics.<sup>146-148</sup>

In Italy, children are assigned to a paediatrician until they are 6 years old; afterwards, the parents can choose to remain with that paediatrician until child is 14 years old or to register the child with a general practitioner. All adolescents over 14 years of age are assigned to a general practitioner. No studies were performed in Italy to compare the prescribing profile of the two kinds of physicians.

Thus, an analysis of drugs prescribed to children 6-13 years old was performed in order to compare general practitioners' with family paediatricians' prescribing profiles.

### **2. Methods**

The analysis involved all paediatric prescriptions reimbursed by the Health Service and dispensed by the retail pharmacies of 15 local health units (LHU) in the Lombardy Region between 1 January and 31 December 2005.

In order to get a comparable sample, only physicians who had in charge children of all the ages in the 6-13 year old age range were included. Moreover, physicians below the 5-centile of the distribution of physicians by number of treated children were excluded. Children receiving six or more prescriptions were also excluded, since the percentage of chronically treated patients may be different between physicians and may influence the prescribing profile.

### 3. Results

A sample of 548,922 children 6-13 years of age was, therefore, included (81% of the Lombardy Region's 6-13 year old population). In all, 402,053 children were cared for by 1020 family paediatricians (88% of the total number of family paediatricians) and 146,869 children were cared for by 2824 general practitioners (42% of the total).

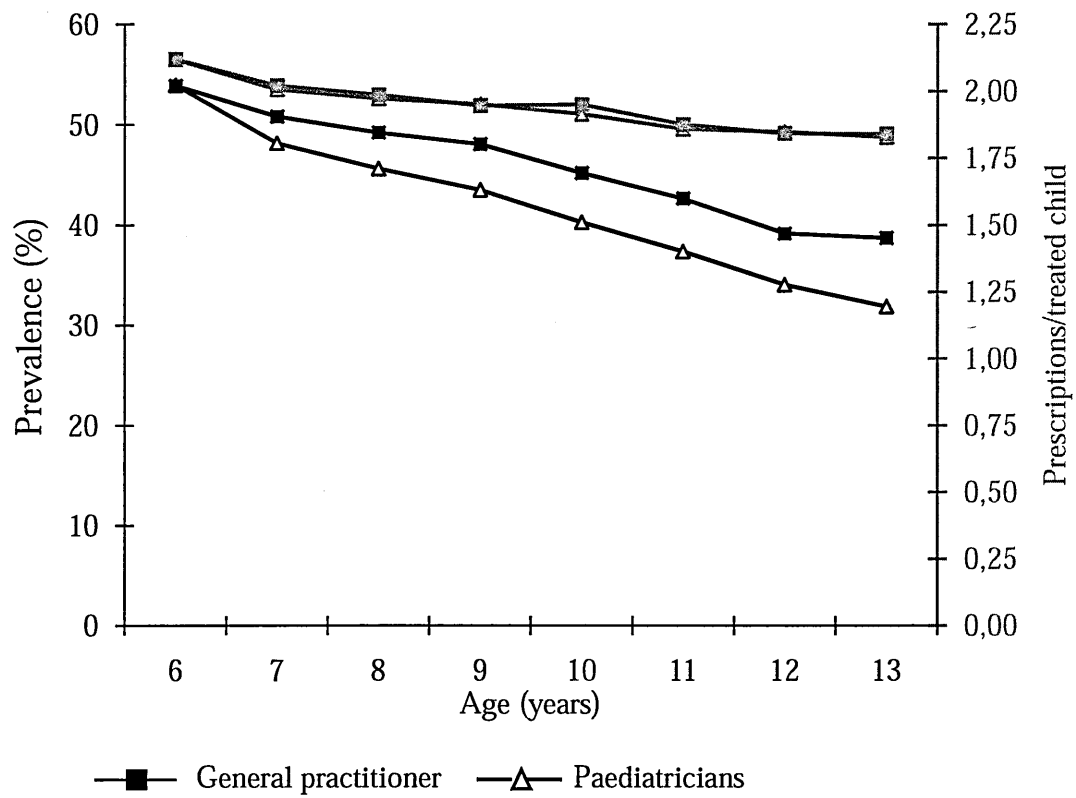
In all, 239,296 children (43.6% of the population) received at least one drug prescription (Table 23). The prevalence was highest at 6 years of age (53.9%), and then decreased to 35% in children 13 years old (Figure 16).

The prevalence was slightly higher in children treated by general practitioners (44.2 versus 43.4%;  $\chi^2_{M-H} = 845$ , d.f. = 1  $p < 0.001$ ). The greatest difference was observed in 13 years old children: 10,799 out of 27,905 (38.7%) children cared for by general practitioners received at least one drug prescription versus 10,543 out of 33,104 (31.8%) children cared for by family paediatricians.

**Table 23 - Characteristics of the population.**

	Family paediatricians	GPs	Total
Physicians (N.)	1020	2824	3844
Children (N.)	402,053	146,869	548,922
Age (ys) (mean±SD)	9±2.2	10.3±2.2	9.3±2.3
M/F	1.04	1.06	1.05
Treated children (N.)	174,335	64,961	239,296
Prevalence (%)	43.4	44.2	43.6
Prescription/treated child	2.0	1.9	2.0
Packages/treated child	2.9	2.6	2.8
Drugs (N.)	499	467	542

Figure 16 - Trend of prevalence by age and kind of physician.



The AUC 6-14 general practitioners/paediatricians prevalence ratio was 1.1.

The chance of receiving a drug prescription, adjusted for age, gender, and LHU of residence, was slightly higher in children cared for by general practitioners (OR 1.16; 95%CI 1.14-1.17). Moreover, the risk was slightly higher for children cared for by female compared to male physicians (OR 1.08; 95%CI 1.07-1.10)

On average, each treated child received 2 prescriptions, without differences between the two physician type groups, while the mean number of medication packages prescribed to children cared for by family paediatricians was slightly higher (2.9 versus 2.6).

Antibiotics, anti-asthmatics, and anti-histamines were the most prescribed therapeutic classes, and covered 92.5% of the packages. The prevalence of antibiotics was nearly

the same in the two groups (37%), while the prevalence of anti-asthmatics was slightly higher in children treated by family paediatricians (10.6 vs 9.9%) and, on the contrary, the prevalence of anti-histamines was higher in the general practitioner treated group (4.2 vs 3.6%).

Taking into account the ten most prescribed classes, the prevalence of antinflammatory and anti-rheumatic drugs was 5-fold higher, and the prevalence of intestinal antidiarrheals/antinfectives was 3.5 fold higher, in children treated by general practitioners.

On the contrary, the prevalence of anti parasitic and of antivirals were 1.4 fold higher in paediatrician treated group.

An analysis of antibiotic prescriptions by class was also performed; the prevalence of penicillins was higher in children cared for by family paediatricians (64.5 vs 54.2%), while the prevalence of macrolides and cephalosporins was higher in children cared for by general practitioners (32.9 vs 28.3%, and 32.2 vs 26.6%, respectively).

Amoxicillin+clavulanic acid was the most prescribed drug independently of the type of physician, followed by amoxicillin and beclometasone. Fourteen out of the 15 most prescribed drugs were the same in both groups (Table 24).

Table 24 -The 15 most prescribed drugs in order of prevalence.

Family paediatricians				General Practitioners			
Drug	Prevalence (%)	Boxes (%)	Prescribers (%)	Drug	Prevalence (%)	Boxes (%)	Prescribers (%)
Co-amoxiclav	15.1	25.8	100.0	Co-amoxiclav	12.5	19.0	96.4
Amoxicillin	10.4	17.7	100.0	Amoxicillin	8.8	12.5	87.9
Beclometasone	6.0	5.5	99.9	Beclometasone	6.0	6.2	83.1
Clarithromycin	5.9	7.5	99.7	Clarithromycin	6.0	7.7	82.3
Azithromycin	4.3	4.7	97.1	Azithromycin	5.1	6.1	71.4
Salbutamol	3.8	3.5	98.8	Cefixime	4.8	6.2	56.6
Cefaclor	3.6	5.9	98.3	Cefaclor	3.6	6.0	63.0
Cefixime	2.7	3.3	96.0	Salbutamol	2.2	2.3	65.4
Cetirizine	2.2	3.3	94.8	Cefibuten	1.9	2.6	39.1
Cefpodoxime	1.5	2.3	76.9	Cetirizine	1.9	3.2	52.8
Ceftibuten	1.4	1.8	87.7	Cefpodoxime	0.9	1.3	24.6
Flunisolide	1.0	0.9	77.3	Flunisolide	0.9	0.9	27.8
Fluticasone	0.9	1.0	83.2	Oxatomide	0.9	0.9	29.5
Budesonide	0.7	0.7	70.7	Cefuroxime	0.8	1.1	19.0
Cefuroxime	0.7	1.0	52.9	Fluticasone	0.7	0.9	26.3
% packages*		84.9				76.9	

\* % of packages covered by the 15 most prescribed drugs. The gray background highlights drugs prescribed by 75% or more physicians.

Budesonide was among the most frequently prescribed drugs only in family paediatrician treated group and oxatomide only in the general practitioner group.

A total of 542 drugs were prescribed, 78% of which were prescribed by both the family paediatricians and the general practitioners. 74 drugs (14%) were prescribed only by the family paediatricians and 42 (8%) only by the general practitioners. In particular, 7/74 and 4/42 were sexual hormones (mainly oral contraceptives). Furthermore, 48 out of 74 (64%) and 36 out of 42 (86%) drugs were prescribed by only one physician to one child. In all, 96% of the drugs were prescribed by less than 25% of the physicians, with a higher percentage among general practitioners compared to family paediatricians (97% versus 92%, respectively,  $\chi^2=11$ ; d.f.=1;  $p=0.0008$ ). In all, 13 drugs were prescribed by 75% or more family paediatricians and only 4 drugs were prescribed by 75% or more general practitioners (table 24).

The drug with the highest degree of concordance was amoxicillin+clavulanic acid, prescribed by more than 96% of family paediatricians and general practitioners. The other common drugs were amoxicillin, beclometasone and clarithromycin. These four drugs covered 68% of the treated children and the 54% of the packages. A total of 91 pharmaceutical preparations (identified by trade name, strength and formulation) containing the four leading drugs was prescribed, 87 of which (96%) were shared by family paediatricians and general practitioners.

Only two pharmaceutical preparations were prescribed by 75% or more family paediatricians and general practitioners: Augmentin<sup>®</sup> (amoxicillin+clavulanic acid) 400/57 mg dry powder for oral suspension and Clenil<sup>®</sup> (beclometasone) 0.8mg/2 ml nebulised suspension. No pharmaceutical preparation containing amoxicillin or clarithromycin was prescribed by more than 50% of the general practitioners.

Among physicians prescribing amoxicillin, 91% of family paediatricians and 44% of the GPs prescribed a generic specialty ( $\chi^2=504$ ; d.f.=1;  $p<0.001$ ). The percentage of children receiving generic amoxicillin was 41% in those cared for by family paediatricians and 22% in those cared for by general practitioners ( $\chi^2=1525$ ; d.f.=1;  $p<0.001$ ).

#### **4. Discussion**

The prevalence of drug prescriptions was slightly higher in children treated by general practitioners with an OR of 1.2. On the contrary, children cared for by paediatricians received a greater number of packages. Despite these differences, the prescription profiles of general practitioners and family paediatricians were similar.

Only a few differences were found concerning the most prescribed therapeutic classes, as expected since the two types of physicians face the same diseases. However, the differences were greater for some classes with a low prevalence, e.g. the prevalence of antinflammatory drugs was 5-fold higher in children treated by general practitioners, even if the most frequently prescribed drugs were the same in both the groups (ketoprofen, nimesulide, acetilsalicylic acid).

A large number of drugs was prescribed, and most of them were prescribed by both family paediatricians and general practitioners. Only a few drugs were specific of a type of physician, and nearly all of them were prescribed by one physician to one child.

It is interesting to note that while 13 drugs were prescribed by 75% or more family paediatricians, only 4 drugs were prescribed by 75% or more general practitioners. A wide variability in the drugs was observed for both groups of physicians, even if a greater percentage of drugs prescribed by less than 25% of the physicians was found for general practitioners (97% versus 92%). A lower concordance was, therefore, observed



between general practitioners, and very few drugs can be considered “essential” on the basis of their prescribing attitude.

It is likely that this finding is influenced by the fact that general practitioners are in charge of a lower number of children compared to family paediatricians and that each general practitioner has to therefore deal with a narrower spectrum of diseases and therapeutic needs.

A low level of agreement emerged also when looking at the pharmaceutical preparations of the 4 drugs with a high degree of concordance among prescribers: 11 preparations were prescribed by 75% or more family paediatricians and only 2 by 75% or more general practitioners. In the case of amoxicillin and clarithromycin there were no pharmaceutical preparations prescribed by more than 50% of the general practitioners. However, this could indicate that many general practitioners prefer to prescribe only one trade name, while family paediatricians more commonly prescribe different trade names of the same drug, as was the case for clarithromycin, for which 3 different trade name oral suspensions were prescribed by more than 75% family paediatricians.

General practitioner seems to have less of a tendency to prescribe generic drugs, at least taking into account amoxicillin prescriptions. In fact, nearly 6 out of 10 general practitioners never prescribed generic amoxicillin and children cared for by general practitioners had a 50% lower chance of receiving generic amoxicillin compared to children cared for by family paediatricians.

The prescribing profile observed in this setting did not differ from that of other Italian contexts, in particular concerning the antibiotic prescription profile, characterized by a wide use of second line agents (cephalosporins or macrolides), in which Italy differs from other European countries.<sup>97</sup>

A more common inappropriate use of antibiotics was observed among general practitioners than family paediatricians in three international studies.<sup>146-148</sup> In this study,

no differences were observed regarding antibiotic prevalence; however, differences were found concerning antibiotic classes, with the family paediatricians prescribing penicillins more commonly and general practitioners prescribing macrolides and cephalosporins more frequently. This finding partly reflects the profile observed in the Italian adult population.<sup>149</sup> Moreover, nearly 1 out of 10 general practitioners never prescribed amoxicillin, which is the first line antibiotic for the most common infections in children. This study therefore seems to confirm that different attitudes towards antibiotic prescribing exist between family paediatricians and general practitioners. However, taking into account other drug classes, family paediatricians and general practitioners seem to share the same inappropriate prescriptions. In this regard, it is interesting to note that the prevalence of nebulised beclometasone, commonly prescribed without evidence of efficacy for the symptomatic treatment of upper respiratory tract infections, was the same in the two groups.

The main limit of this study is that only drugs reimbursed by the national health service were evaluated. It is therefore possible that there are some differences in the prescribing profile of drugs non reimbursed or over the counter (e.g. analgesics, antitussive medicines, and prokinetics). Moreover, this study was performed in a very homogeneous regional setting and the findings may not perfectly reflect the national situation. However, the study sample represents 12% of the 6-13 year old Italian population and the profile of drug prescriptions is similar to that observed in other national settings.

The findings from this study seem to document that there are few differences in the prescribing pattern between general practitioners and family paediatricians. Differences exist in particular for older children and for some drug classes. The inappropriateness of drug prescription to children is mostly independent from the type of physician. This should be taken into account in planning and performing educational interventions with

the aim to improve the rational use of drugs in children. Such interventions should involve all the health care professionals and not only family paediatricians.

**X. CONCLUSIONS**

Quantitative and qualitative differences were found in drug prescribing in children and adolescents between countries, regions, local health units and even areas of the same city. Despite the differences, a prescribing profile specific to Italy was observed in all the settings, characterised by extensive use of antibiotic and anti-asthmatic drugs. The different drug prescription prevalence appears to be mainly related to different prescribing attitudes in Italian physicians.

The differences observed between local health units suggest that educational interventions for health care professionals and parents may be effective in improving rational drug use. However, more efforts are also needed in certain contexts characterised by a low prevalence, but associated with inappropriate drug use.

The studies described in this thesis suggest that pharmacoepidemiology is a valuable tool for monitoring the appropriateness of drug prescribing. However, the epidemiological evaluation of drug prescriptions in children should be improved, with regards to the methodological quality of studies. Nearly all the drug utilization studies were retrospective or cross-sectional and scant data are available on the overall cumulative drug exposure during childhood. A prospective cohort study of drug prescriptions for children should be performed including children receiving chronic drug therapy.

Merging different administrative databases (e.g. prescription, hospitalisation, specialist physician databases) may overcome the lack of information concerning the diseases for which drugs are prescribed and may provide useful details for evaluating diagnostic and therapeutic approaches.

Finally, multinational collaborative studies are needed with the aim to collect valid and comparable data, to improve the rational use of drugs and to guarantee to children and their family safe, and effective drug therapies.

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## **XII. PUBLISHED MATERIAL ARISING FROM THE PROJECT**

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